ARCHIVES of INTERNAL MEDICINE

VOLUME 73 JUNE 1944 NUMBER 6

COPYRIGHT, 1944, BY THE AMERICAN MEDICAL ASSOCIATION

CLINICOPATHOLOGIC STUDIES OF RENAL DAMAGE DUE TO SULFONAMIDE COMPOUNDS

A REPORT OF FOURTEEN CASES

FRANCIS D. MURPHY, M.D.; JOSEPH F. KUZMA, M.D.; THEODORE Z. POLLEY, M.D., AND JOHN GRILL, M.D.

MILWAUKEE

It has become widely recognized that the kidney may be damaged in the course of therapy with sulfonamide compounds. Such renal complications may be classified roughly as follows: 1. Mechanical complications produced by masses of crystals of the sulfonamide compounds in the kidneys, pelves and ureters. These lead to obstructive lesions. This group may be further subdivided into (*a*) the extranephric, in which the concretions causing obstruction are within the pelves of the kidney or in the ureters, and (*b*) the intranephric, in which the concretions are in the kidney substance itself. 2. Toxic intrarenal lesions without mechanical obstruction. These lesions occur within the kidney and are not associated with mechanical obstruction but may be attributed to the toxic effect of the sulfonamide compound on the parenchymal tissue. This class may be divided into three groups, which represent different phases of the same reaction and are not distinct divisions: (*a*) simple tubular degeneration; (*b*) necrotic tubular degeneration, and (*c*) glomerular changes. In some instances there may be evidence of obstruction and toxic parenchymal changes in the same kidney.

Shortly after the sulfonamide compounds came into general use, the mechanical or obstructive lesions were diagnosed and treated adequately. Nonobstructive toxic changes in the kidney were recognized a little later, and during the past few years a considerable number of such cases have been reported in the literature.[1] The combination forms have also been observed and commented on.[2] While the injuries of the kidneys caused by mechanical blocking of the urinary passages are the most common of all, the renal damage that occurs independently of obstruction is apt to be more serious. The reason for this is that the obstructive masses may be removed mechanically while the toxic injuries are not so amenable to treatment. Renal injury due to sulfonamide compounds requires prompt and early recognition of the damage, and this applies particularly to the toxic effects.

The purpose of this paper is to report the clinical and pathologic data for 14 patients, in all of whom renal damage developed after therapy with sulfonamide compounds.

CLINICAL FEATURES

The observations on the 14 patients studied were made in the period from January 1939 to

Presented before the Sixteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 5, 1943.

From the Department of Medicine, Marquette University School of Medicine, and the Medical Clinics and Department of Pathology, Milwaukee County General Hospital.

1. (*a*) Murphy, F. D., and Wood, W. D.: Acute Nephritis and the Effect of the Sulfonamides on the Kidneys, Ann. Int. Med. **18**:999-1005 (June) 1943. (*b*) Merkel, W. C., and Crawford, R. C.: Pathologic Lesions Produced by Sulfathiazole: Report of Four Fatal Cases, J. A. M. A. **119**:770-776 (July 4) 1942. (*c*) Lederer, M., and Rosenblatt, P.: Death During Sulfathiazole Therapy, ibid. **119**:8-18 (May 2) 1942. (*d*) Winsor, T., and Burch, G. E.: Renal Complications Following Sulfathiazole Therapy, ibid. **118**:1346-1353 (April 18) 1942. (*e*) Cutts, M.; Burgess, A. M., and Chafee, F. H.: Treatment of Lobar Pneumonia with Sulfathiazole and Sulfapyridine, New England J. Med. **223**:762-764 (Nov. 7) 1940. (*f*) Finland, M.; Peterson, O. L., and Goodwin, R. A., Jr.: Sulfadiazine: Further Clinical Studies of Its Efficacy and Toxic Effects in 460 Patients, Ann. Int. Med. **27**: 920-934 (Dec.) 1942. (*g*) Tragerman, L. J., and Goto, J. M.: Fatal Reactions to Administration of Sulfonamide Drugs: Report of Five Cases, J. Lab. & Clin. Med. **25**:1163,1176 (Aug.) 1940. (*h*) Eggleston, C., and Weiss, S.: The Urinary Tract in Sulfonamide Therapy, Am. J. M. Sc. **202**:757-772 (Nov.) 1941. (*i*) Bradford, H. A., and Shaffer, J. H.: Renal Changes in a Case of Sulfadiazine Anuria, J. A. M. A. **119**:316-318 (May 23) 1942. (*j*) Jeck, H. S., and Orkin, L.: Toxic Renal Reactions Following the Use of Sulfadiazine, J. Urol. **49**:290-301 (Feb.) 1943.

2. (*a*) Erganian, J. A., and Doval, J. H.: Fatal Anuria Following Administration of Sulfonamides with Reference to Tubular Necrosis and Regeneration, J. Lab. & Clin. Med. **28**:808-812 (April) 1943. (*b*) Hellwig, C. A., and Reed, H. L.: Fatal Anuria Following Sulfadiazine Therapy, J. A. M. A. **119**:561-563 (June 13) 1942. (*c*) Jeck and Orkin.[1j]

September 1943. This clinical study will emphasize the following features: (1) the disease for which the patient was treated; (2) the kind of sulfonamide compound and the amount of the drug given to each patient; (3) the largest, the average and the smallest total dose administered; (4) the first evidence of renal damage noted; (5) the subsequent course of the renal disorder; (6) the maximum blood levels of the drug at the time of renal injury and their variations, and, finally, (7) the cause of death and the postmortem diagnosis. These data are summarized in the tables.

Of the 14 patients, 4 were male and 10 were female. The oldest was 64 years old; the youngest, 1 year. The others ranged from 19 to 61 years of age. Three of the 14 patients were given sulfonamide compounds for infections of the upper respiratory tract, 1 for erysipelas, 4 for lobar pneumonia, 1 for bronchopneumonia,

TABLE 1.—*Clinical Data in Fourteen Cases of Renal Insufficiency Due to Intoxication with Sulfonamide Compounds*

Case No.	Initials	Age, Yr.	Sex	Occupation	Drug	Total Amount Given, Gm.	Disease Treated	Maximum Blood Level of Sulfonamide Compound, Mg. per 100 Cc.	Urinary Findings
1	C. G.	56	F	Housewife	Sulfathiazole	18	Infection of upper respiratory tract	....	Albumin, +++ WBC, loaded RBC, many Casts, none Crystals, none
2	M. S.	51	F	Housewife	Sulfathiazole Sulfadiazine	22 6	Infection of upper respiratory tract, with acute streptococcic sore throat	16.6	Albumin, ++++ WBC, 2-5/h. p. f. RBC, 25/h. p. f. Casts, none Crystals, none
3	E. T.	25	F	Housewife	Sulfathiazole	15	Streptococcic septicemia	16.7	Albumin, + WBC, few RBC, few to many Casts, few, granular Crystals, none
4	A. P.	51	F	Inmate of infirmary	Sulfathiazole	15.5	Cystopyelitis	6.7	Albumin, +++ WBC, 8-10/h. p. f. RBC, loaded Casts, many Crystals, none
5	A. B.	28	F	Housewife	Sulfanilamide	41	Septicemia secondary to septic endometritis	9.6	Albumin, none WBC, few RBC, none Casts, many Crystals, none
6	L. S.	44	M	Laborer	Sulfadiazine	38	Lobar pneumonia; pulmonary abscess	11.0	Albumin, ++ WBC, many RBC, 20-25/h. p. f. Casts, none Crystals, many
7	L. D.	45	F	Asylum inmate	Sulfanilamide	20	Erysipelas; chronic nephritis	15.0	Albumin, ++ WBC, loaded RBC, few Casts, granular, coarse Crystals, 4-5/h. p. f.
8	S. M.	61	M	Laborer	Sulfathiazole Sulfacetimide	34 26	Pneumonia of lower lobe of left lung	7.3	Albumin, ++ WBC, 3-4/h. p. f. RBC, many Casts, none Crystals, many
9	F. W.	56	M	Laborer	Sulfadiazine	20	Lobar pneumonia	3.9	Albumin, ++ WBC, none RBC, many Casts, 1-2/h. p. f. Crystals, many
10	M. M.	1	M	.....	Sulfathiazole	0.65 (10 grains)	Gastroenteritis	....	Crystals, loaded
11	L. V.	64	F	Saleswoman	Sulfathiazole	6	Infection of upper respiratory tract	12.4	Albumin, ++++ WBC, 14-18/h. p. f. RBC, many Casts, many, granular and hyaline Crystals, none
12	M. S.	19	F	Housewife	Sulfanilamide	10	Sepsis	....	Albumin, ++++ WBC, 7-10/h. p. f. Casts, granular and hyaline
13	M. S.	19	F	Housewife	Sulfathiazole	30	Pneumonia	6.6	Albumin, +++ WBC, 1-2/h. p. f. Casts, 1-4/h. p. f., granular Crystals, many
14	G. S.	38	F	Housewife	Sulfadiazine	34	Bronchial pneumonia	12.5	Albumin, + WBC, 1-2/h. p. f. RBC, loaded Casts, few Crystals, many

1 for cystopyelitis, 3 for streptococcic septicemia and 1 for gastroenteritis (table 2). Of the sulfonamide compounds employed, sulfathiazole was the one of choice and was used in 7 cases. Sulfadiazine was given with sulfathiazole in 1 case, sulfadiazine alone in 2, sulfanilamide in 3 and sulfacetimide (acetylsulfanilamide) with

TABLE 2.—*Disease Treated and Sulfonamide Compound Used*

Disease Treated	Number of Cases
Infection of upper respiratory tract	3
Gastroenteritis	1
Erysipelas	1
Lobar pneumonia	4
Bronchopneumonia	1
Cystopyelitis	1
Septicemia	3

Sulfonamide Compound Used	Number of Cases	Average Dose of Each Sulfonamide Compound, Gm.
Sulfathiazole	7	15.8
Sulfathiazole (with sulfadiazine)	1	6.0
Sulfadiazine	2	31.0
Sulfanilamide	3	18.0
Sulfacetimide (with sulfathiazole)	1	26.0

Smallest single total dose used, 10 grains (0.65 Gm.) of sulfathiazole

sulfathiazole in 1. The usual method of administration was followed for all patients; that is, 2 to 3 Gm. of the drug was given at once and 1 Gm. thereafter every four hours until it was discontinued for some reason. The largest total dose in any case was 41 Gm. of sulfathiazole, and the smallest was 10 grains (0.65 Gm.) of the same drug. The average total amount of sulfonamide compounds given before evidence of renal damage appeared was 20 Gm. Judging from these observations, the quantity of the drug used bears little or no relation to renal injury.

TABLE 3.—*Evidence of Renal Damage*

Number of patients exhibiting renal damage before therapy	Albuminuria	5 cases
First evidence of renal damage after therapy was begun	Oliguria	12 cases
	Anuria	1 case
	Generalized edema	1 case
	Crystals, Red blood cells, Casts, Albumin	with oliguria, 5 cases
	Red blood cells, Casts, Albumin	with oliguria, 7 cases; with anuria, 1 case
	Debris	with anuria, 1 case
Blood levels of drug at onset of renal damage	Varied between 3.9 Mg. per 100 Cc. to 16.7 Mg. per 100 Cc.	

Five of the patients had mild albuminuria without other evidence of renal involvement before the drug was administered (table 3). This was considered no contraindication to the use of sulfonamide compounds, as sometimes renal impairment not only does not become worse but clears during treatment with sulfonamide drugs.[3] Concerning the 14 patients under study, there was no correlation between the presence of albumin in the urine and the speed with which subsequent oliguria and anuria developed. The average time for the development of signs of serious renal damage was four days. Oliguria was the first evidence of severe renal insufficiency in 12 cases, anuria in 1 case and generalized edema in 1. In 5 cases, red blood cells, granular casts, albuminuria, and crystals of the sulfonamide compound were found associated with the oliguria. In 7 cases of oliguria, red cells, casts and albumin were present but crystals were absent. Retention of nitrogenous substances in the blood was observed in all but 4 cases. The nonprotein nitrogen content ranged from 60 to 218 mg. per hundred cubic centimeters (table 4). The blood pressure was normal in all cases of this series, except in 1 in which glomerular involvement dominated the pathologic picture post mortem. In this case the blood pressure was abnormally high. In the other cases, there was no significant change of

TABLE 4.—*Nonprotein Nitrogen Content of the Blood*

Evidence of Nitrogen Retention: Day of Onset of Nitrogen Retention After Therapy Was Begun	Ten Cases	
	Nonprotein Nitrogen Levels, Mg. per 100 Cc.	Creatinine Levels, Mg. per 100 Cc.
6th	176.5, 200.0, 218.5	4.0, 4.0, 4.2
5th	60.0	1.5
5th	85.6, 92.3	2.3, 2.5
12th	85.6, 86.9	3.0
6th	75.9, 80.0	3.6, 4.8
2d	92.3	
4th	96.0, 128.4	3.19, 3.33
7th	62.8	
7th	135.0	
5th	62.4, 140.0	5.6

the blood pressure during the course of renal insufficiency.

The level of the sulfonamide compound in the blood was determined in all cases, but no correlation could be made between the height of the blood level and the type of damage sustained by the kidneys. As illustration, 1 patient with a blood level of the drug of 16.7 mg. per hundred cubic centimeters exhibited nephrotoxic changes consisting of simple tubular degeneration, while in other cases, in which more severe damage was seen, the blood level was relatively much lower. Two patients showed the combination form of nephrotoxic and obstructive changes. In 1 the damage was caused by sulfathiazole and in the other by sulfadiazine.

3. Fishberg, A. M.: The Use of Sulfonamides in Renal Insufficiency, J. Mt. Sinai Hosp. **8**:509-513 (Jan.-Feb.) 1942. Williams, R. H.; Longcope, W. T., and Janeway, G. A.: The Use of Sulfanilamide in the Treatment of Acute Glomerulonephritis, Am. J. M. Sc. **203**:157-172 (Feb.) 1942. Murphy and Wood.[1a]

Of 14 patients, 5 died of uremia due to intoxication with the sulfonamide compound and 1 of uremia due to nephritis. One died of streptococcic septicemia; another, of septicemia secondary to septic endometritis, and 1, of sepsis with generalized peritonitis. Lobar pneumonia, in 1 case complicated by pulmonary abscess, accounted for 2 deaths and bronchopneumonia for 1. One patient died of portal cirrhosis associated with heart disease. The fourteenth patient (case 8 [S. M.]) survived after decapsulation of the kidney; but, as a section of the kidney was removed for biopsy, the case of this patient is incorporated with those of the 13 who died (table 5).

TABLE 5.—*Cause of Death of 14 Patients Treated with Sulfonamide Compounds*

Subject	Initial	Cause of Death
1	C. G.	Uremia due to sulfathiazole intoxication
2	M. S.	Uremia due to sulfathiazole intoxication
3	E. T.	Streptococcic septicemia
4	A. G.	Uremia due to sulfathiazole intoxication superimposed on intracapillary glomerulosclerosis of diabetes
5	A. B.	Septicemia secondary to septic endometritis
6	L. S.	Lobar pneumonia with pulmonary abscess
7	L. D.	Uremia due to nephritis
8	S. M.	Survived
9	F. W.	Lobar pneumonia
10	M. M.	Uremia due to sulfathiazole intoxication
11	L. V.	Uremia due to sulfathiazole intoxication
12	M. S.	Sepsis with generalized peritonitis
13	M. S.	Bronchopneumonia
14	G. S.	Portal cirrhosis with obesity heart disease

REPORT OF CASES

The study of our cases leads us to believe that there are three chief types of nephrotoxic damage of the renal parenchyma. Undoubtedly these are illustrative of different degrees of the same pathologic process. Since the clinical features followed closely the same general pattern, 3 cases are given, each representing the clinical and pathologic phase peculiar to one of the types of nephrotoxic reaction found. Case 1 exemplifies the simple type of damage to the kidney due to toxic effects of sulfonamide compounds associated with obstruction. Case 2 represents the group characterized by extensive tubular degeneration with necrosis of the pyramids. The third case report is typical of the type in which extensive glomerular involvement is found in addition to widespread tubular injury.

CASE 1.—L. S., a man aged 44, entered the hospital complaining of hemoptysis and pain in the right side of the chest of five days' duration. The pain in the chest was accentuated by coughing, deep breathing and sneezing and was associated with fever, sweats, fatigue and weakness. The patient had had a loss of weight of 12 pounds (5.4 Kg.) in the past month.

Physical examination revealed a ruddy-faced, perspiring, well developed and well nourished white man, who appeared ill but in no respiratory distress. The blood pressure was 110 systolic and 60 diastolic. The temperature was 102 F., the pulse rate 96 and the respiratory rate 24 per minute. The chest exhibited limited expansion, impaired percussion note, depressed breath sounds and a friction rub over the right lower portion anteriorly and posteriorly. Large moist rales were heard throughout the right side of the chest, predominantly at the right apex. A clinical impression of pneumonia of the lower lobe of the right lung was made.

The erythrocyte sedimentation rate was 122 mm. in one hour and 126 mm. in two hours.

The roentgenogram of the chest revealed a partial consolidation of the lower half of the right pulmonary field.

Urinalysis revealed nothing abnormal.

In addition to general supportive measures, the patient was given sulfadiazine, 2 Gm. at once followed by 1 Gm. every four hours with equal doses of sodium bicarbonate. He continued to have a temperature ranging between 100 and 102 F. Sulfadiazine was tolerated well, and the complaints were minimal except for that of a productive cough. The sulfadiazine level three days after his entry was 10.2 mg. per hundred cubic centimeters. The urine on repeated microscopic examinations revealed no crystals, red cells or white cells.

On the ninth day after treatment was begun, the patient did not urinate. Catheterization at first yielded no urine, but later in the day approximately 1 ounce (30 cc.) of urine containing numerous red and white blood cells was passed. The sulfadiazine level of the blood was 11 mg. per hundred cubic centimeters. Determinations of blood chemistry showed a nonprotein nitrogen content of 62.8 mg. and a creatinine content of 5 mg. per hundred cubic centimeters. Up to this time the patient had received a total of 38 Gm. of sulfadiazine.

Use of sulfadiazine was discontinued immediately. Fluids in the form of 5 per cent dextrose were given both orally and parenterally at the rate of 1,000 cc. every four hours, but diuresis did not follow. A diagnosis of sulfadiazine obstruction was made. Cystoscopy was performed, and the washings from the bladder revealed numerous sulfadiazine crystals. Intravenous urograms indicated no definite abnormalities. A left posterior nephrostomy was done, but it was of little avail, though the patient did begin to void. Examination of the urine showed albumin (2 plus), occasional red blood cells and white blood cells and many sulfadiazine crystals. The course was retrograde, and the patient died approximately twenty-four hours after operation.

Autopsy Report.—Conditions observed at autopsy were most significant in the liver, lungs and kidneys. The left kidney measured 18 by 9 by 7 cm., and weighed 550 Gm. The lower half of the organ was replaced by a large, lobulated, hemorrhagic, yellowish tumor. The capsule was loose. Throughout the cortical tissue there were numerous petechial hemorrhages and linear hemorrhagic streakings. Some of the pyramids were streaked with gritty, grayish, radiating lines extending toward the cortical tissue in a fanlike manner. The calices, pelvis and ureter contained a large amount of orange red sandlike concretions. At the ureteropelvic junction some of this material was firmly impacted, producing an obstruction and dilatation of the pelvis.

The right kidney weighed 330 Gm. and similarly had a 2.5 cm. yellowish red hemorrhagic tumor at the lower pole. The width of the cortex measured

12 mm. The gross observations were essentially the same as those of the left kidney. The proximal third of the ureter was completely obstructed by an impacted mass of concretions. The perirenal and hilar tissues of both kidneys were edematous. Similar orange red concretions were found in the urinary bladder. Above the left ureteral orifice were two grayish yellow necrotic plaques. The mucous membrane of the entire kidney-urinary bladder tract was injected and granular.

Microscopic examination revealed a bilateral hypernephroma. The concretions corresponded in structure to acetylated sulfadiazine. Aside from this, the kidney substance exhibited considerable degenerative changes in the convoluted tubules. Many of the epithelial cells were without nuclei and were greatly swollen, granular and vacuolated. Other tubular epithelium was desquamated (fig. 1). The collecting tubules were filled with amorphous debris, consisting of cell detritus, proteins and sulfadiazine precipitates in noncrystalline form. Many glomeruli showed swollen tufts which filled out Bowman's space. All of the interstitial tissue was edematous and sparingly infiltrated by polymorphonuclear cells.

The liver weighed 2,440 Gm. Its capsule was tense and glistening, and the liver tissue was fatty, yellow and soft, with pronounced swelling of the lobular structure. Many of the cut surfaces were stippled with petechial hemorrhages. Microscopically the hepatic cord cells revealed swelling and granularity. Many were distended by large globules of fat. Occasionally areas of focal necrosis were seen. In such places the hepatic cells were replaced by an accumulation of inflammatory cells. Kupffer cells in general were swollen.

The lungs showed both gross and microscopic evidence of lobar pneumonia in the stage of gray hepatization.

CASE 2.—C. G., a 56 year old white woman, was admitted to the hospital in a state of semicoma. The patient, known to have diabetes with albuminuria, acquired an infection of the upper respiratory tract with bronchitis three days before entry, for which she was given sulfathiazole, 1 Gm. every four hours up to the time of admittance. Two days before entry she became grossly confused, and a day before her admission to the hospital a definite oliguria developed.

Physical examination revealed an extremely obese white woman, 56 years of age, pallorous and jaundiced and with a uremic odor to the breath. She was restless and confused. The blood pressure was 118 systolic and 64 diastolic. The temperature (rectal) was 98 F; the respiratory rate was 24 per minute and the pulse rate 92 per minute. A left apical systolic murmur was present, and the liver was palpable.

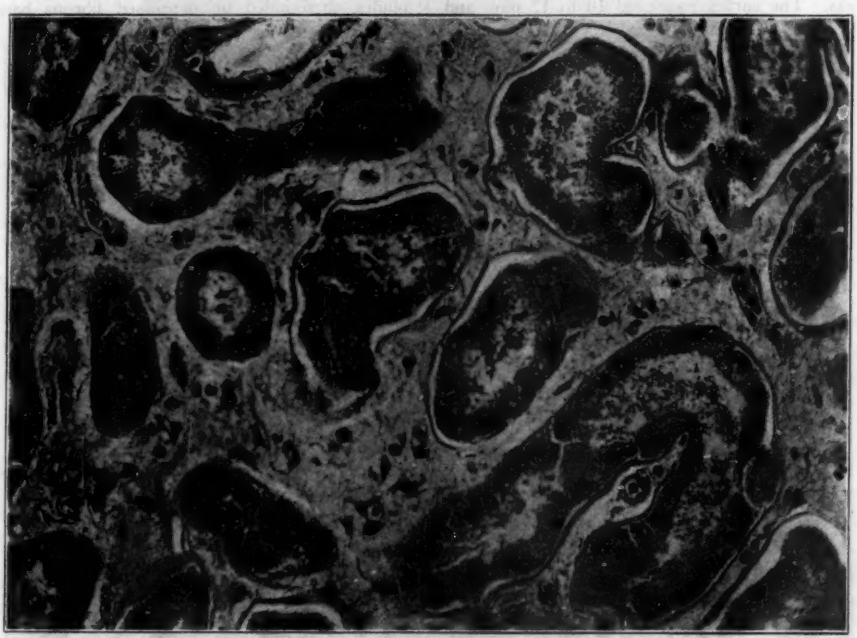


Fig. 1.—Tubular degeneration. The tubules are separated from each other by an edematous interstitial tissue. Many of the tubular epithelial cells have lost contact with the basement membrane and are greatly swollen, granular and vacuolated. The nuclei are absent in some cells and pyknotic in others. In some instances the tubular epithelium is condensed into a hyperchromatic mass of cells having the appearance of a giant cell. Hematoxylin and eosin; approximately 350 diameters.

Examination of the urine revealed a 3 plus reaction for albumin, numerous white blood cells and 5 to 10 red blood cells per high power field. On entry, the red blood cell count was 2,850,000, with 7.5 Gm. of hemoglobin, and the white blood cell count was 28,700, with 66 per cent stab forms and 24 per cent segmented forms. Chemical studies of the blood done at the same time showed a sugar content of 425 mg. per hundred cubic centimeters, a nonprotein nitrogen content of 96 mg. and a creatinine content of 3.19 mg.

Despite the giving of approximately 2,500 cc. of fluid intravenously every day, the oliguria persisted. The nonprotein nitrogen content rose to 128.4 mg. per hun-

dred cubic centimeters, and the carbon dioxide–combining power of the blood dropped to 42.8 volumes per cent. The patient grew steadily worse and became more confused, dyspneic and lethargic. She passed only 50 cc. of urine during the terminal forty hours. On her fourth day in the hospital she died in a state of uremia.

Autopsy Report.—At necropsy interesting gross changes were found in the kidneys. Both organs were greatly enlarged, having a combined weight of 600 Gm. As soon as the capsule was opened, the swollen, shiny, tense kidney substance bulged through. Between the capsule and the kidney substance a free fluid had accumulated. The cortical surface was glistening and smooth. Many petechial hemorrhages were visible on the surface. On section, the swollen, edematous tissue was seen to be mottled with large grayish and hemorrhagic areas. The cortex measured 10 to 12 mm. and cells desquamated into the lumen, forming intraluminal pseudo giant cells. Pus casts filled many of the tubules. Other tubules nearer the areas of reaction were more affected, and small areas of tissue were destroyed by foci of granuloma-like accumulations. These collections were composed of monocytic cells resembling epithelioid cells, numerous lymphocytes, polymorphonuclear cells and occasional eosinophils. At times these cells were seen about blood vessels and were accompanied by multinucleated giant cells (figs. 3 and 4). Some of the vessels had closely applied giant cells completely surrounding the circumference of the vessel (fig. 5). The glomeruli revealed arteriosclerotic changes of hyalinization of the tufts and afferent vessels.

The liver consistence was increased, and the surface appeared granular. The cut surface likewise presented a granular appearance due to the enlarged elevated lobules surrounded by depressed fibrous bands. The

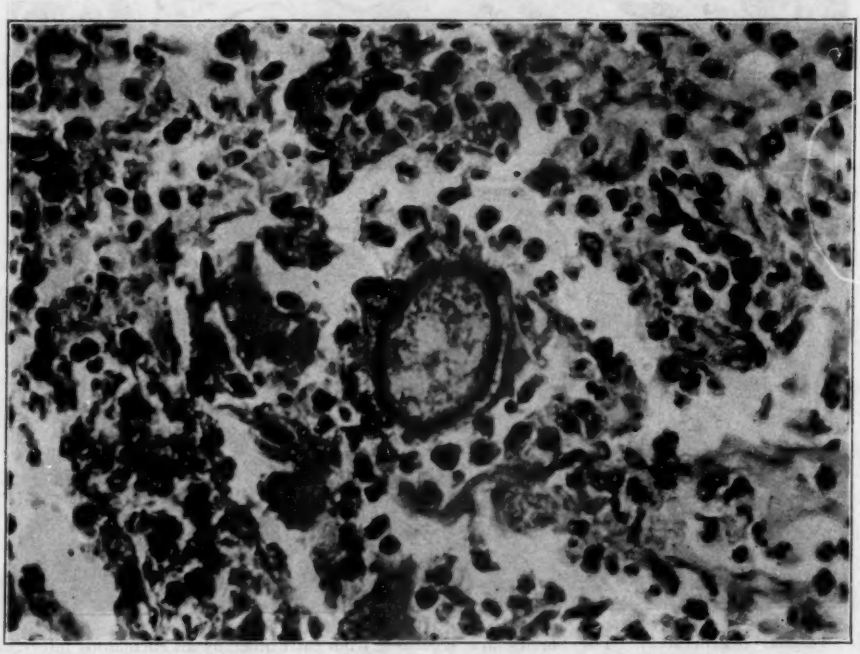


Fig. 3.—Perivascular distribution of the inflammatory cells. Many of the cells are polymorphonuclears, lymphocytes, plasma cells and epithelioid cells. The vessel wall itself is undergoing degeneration. Hematoxylin and eosin; approximately 700 diameters.

was streaked with numerous linear hemorrhages and petechiae. All of the pyramids were bulging, dull grayish and soft. The tissue of the pyramids showed complete necrosis but no evidence of any concretions (fig. 2). All of the perirenal and hilar tissues were edematous.

Microscopic study of the kidney tissue revealed extensive necrosis of the pyramids. Such areas were represented by massive cellular disintegration. All tubular epithelium was lost; only the edematous, distorted interstitial tissue remained. The area between the viable cortical tissues and the necrotic pyramids was represented by a highly cellular reaction. Many of the cells of this zone were polymorphonuclear leukocytes. The viable tissue of the cortex and the columns of Bertini showed numerous hemorrhages and pronounced vascular engorgement. Many of the convoluted tubules were greatly swollen and the epithelial conditions observed microscopically were those of portal cirrhosis with fatty infiltration and degeneration of the hepatic cells. In many areas small foci of necrosis were visible in the lobules. The cells in these foci were polymorphonuclear leukocytes, lymphocytes, monocytic cells, eosinophils and plasma cells. Pronounced swelling of the Kupffer cells was evident.

CASE 3.—M. S., a 51 year old white woman, entered the hospital complaining of a sore throat of four days' duration. The day prior to her entry to the hospital her private physician gave her sulfathiazole, 1 Gm. every four hours, with equal doses of sodium bicarbonate for an infection of the upper respiratory tract with acute streptococcic sore throat.

On entry to the hospital the patient had a temperature of 102 F., a pulse rate of 120 and a blood pressure of 114 systolic and 70 diastolic. On inspection she appeared toxic and febrile. The pupils were equal and reacted

Fig. 2.—Gross. Kidney on hemisection. The entire organ is greatly enlarged, glistening and streaked with hemorrhages. Both the cortex and the pyramids are bulging. The cortical tissue is wide, soft and edematous. All pyramids are necrotic. The gray-yellow necrosis involves most of the pyramid substance. The mucous membrane of the calices and pelvis likewise is hemorrhagic.

to light. The throat was of a beefy, dry color. There was no nuchal rigidity, and there were no palpable lymph nodes. The chest was essentially normal. The heart beat was rapid and regular, and a systolic murmur was heard at the base. The abdomen was distended, and there was some tenderness at both costovertebral angles. The upper and lower extremities plus the torso exhibited numerous erythematous papules, some with small areas of vesiculation and others with large blotches of erythema.

The patient was given sulfathiazole, 2 Gm. every four hours, with equal doses of sodium bicarbonate. A study of the blood revealed a normal red cell count and a white cell count of 27,500, 21 per cent of which were stab forms, 61 per cent segmented forms and 18 per cent lymphocytes.

The urine on entry showed a 2 plus reaction for albumin and only 2 leukocytes per high power field.

Staphylococci and nonhemolytic streptococci were present in the culture of material from the throat.

After the first twenty-four hours, sulfathiazole was reduced to 1 Gm. every six hours. On the patient's second day in the hospital the blood sulfathiazole level was 10.4 mg. per hundred cubic centimeters. The urine showed a 4 plus reaction for albumin and approximately 25 red blood cells per high power field. On this day use of sulfathiazole was discontinued and administration of sulfadiazine was begun, 0.5 Gm. every six hours. The temperature continued to rise and ranged between 102 and 105 F. rectally. On the third hospital day, the level of sulfonamide compounds in the blood was 16.6 mg. per hundred cubic centimeters. The urine continued to show a 4 plus reaction for albumin, and there was a great increase in the number of red cells. No crystals of sulfadiazine were seen. On the fifth hospital day oliguria was noted, and shortly afterward a drug rash developed. The use of sulfadiazine was discontinued, and fluids were forced parenterally as well as orally. The patient responded poorly.

By the eighth day in the hospital the patient had lapsed into a state of coma. The temperature (rectal) continued to spike between 101 and 104.5 F., and the oliguria became more pronounced. On the twelfth hospital day, the nonprotein nitrogen level had risen to 140 mg. per hundred cubic centimeters, and the creatinine level was 5.6 mg. The coma became more profound, and the patient began to have edema of the lower extremities. The blood picture revealed a slowly progressive anemia, with the red blood cell count falling to 3,700,000 and the hemoglobin content to 60 per cent on the thirteenth hospital day. The urinary picture continued to show a 4 plus reaction for albumin, numerous red blood cells and white blood cells and many granular casts. In spite of alkalinization, parenteral administration of fluids and general supportive measures, the patient died in a state of uremia on the thirteenth day after entry to the hospital.

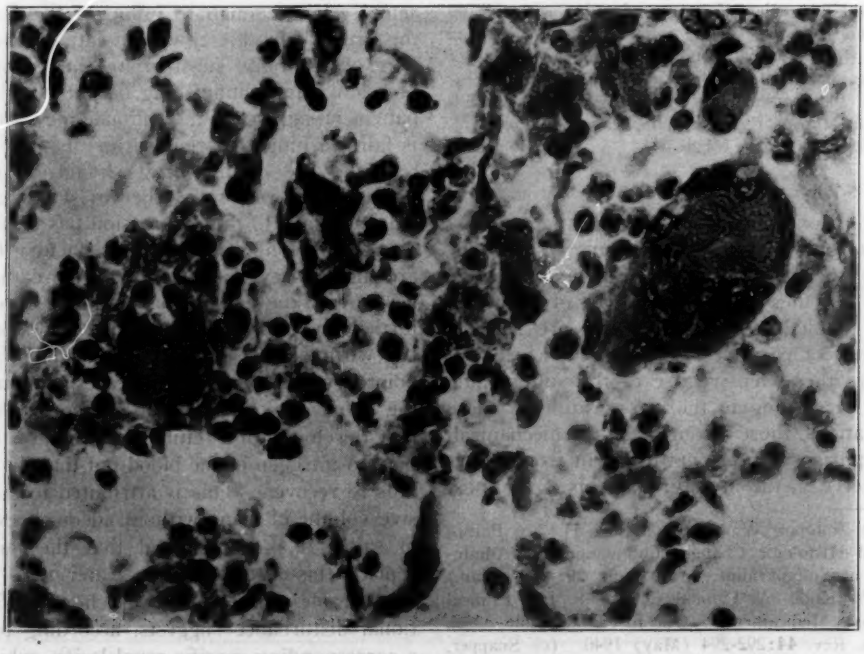


Fig. 4.—Giant cells in a granuloma-like focus. These giant cells are found in addition to the cellular Complement of figure 3. They arise from the epithelioid cells that may also be seen in the photograph. Hematoxylin and eosin; approximately 700 diameters.

Autopsy Report.—The right kidney was swollen and weighed 260 Gm. The cortical surface was smooth and glistening and stippled with petechial hemorrhages. Throughout the congested, swollen, cut surface, there were yellowish gray pinpoint elevations. These were found in the columns of Bertini. The total cortex measured 10 to 12 mm. in width. The pelvis and calices had a swollen, hemorrhagic mucous membrane.

The left kidney weighed 330 Gm. The substance was deeply congested and speckled with minute dots as seen in the right kidney. Many pyramids were grayish. Microscopic changes were those of moderately

advanced tubular degeneration involving particularly the convoluted tubules. Some of the collecting tubules, however, were filled with cellular debris and broken down polymorphonuclear cells. In the interstitial tissue small collections of polymorphonuclear cells, lymphocytes and plasma cells were found. Most pronounced changes, however, were limited to the glomeruli, which had advanced changes of hyalinization as described in intracapillary glomerulosclerosis of persons with diabetes who are past 40 years in age. In addition, many tufts were greatly distended by polymorphonuclear cells, lymphocytes and plasma cells. The epithelial cells were swollen and proliferating. Most glomeruli completely obliterated Bowman's space, and some had well developed epithelial crescents infiltrated by numerous polymorphonuclear cells (fig. 6). In some instances the glomerular tufts blended almost imperceptibly with Bowman's capsule. The afferent arterioles were thickened and hyalinized.

The liver was enlarged, fatty and granular, weighing 2,300 Gm. The cut surface was of a tan color and speckled with petechial hemorrhages and some larger hemorrhagic foci. The lobules were indistinct. Microscopically the significant observations were focal cellular infiltrations of polymorphonuclears, lymphocytes and plasma cells in the lobules.

COMMENT

Of the numerous toxic complications caused by sulfonamide compounds, injury to the kidneys is the most serious. Safeguarding the kidneys becomes an important part of the treatment. While these complications are serious, they are comparatively uncommon when one considers the extensive use of the sulfonamide drugs. According to the classification of these complications, those belonging in the mechanical, extranephric group are not different from others encountered in the literature.[4] This is the most common type of renal injury and responds best of all to therapeutic measures. When obstruction occurs within the kidney, a cure is not as easily accomplished, although retrograde lavage and discontinuation of the drug should always be done. Precipitation of the sulfonamide compound is the etiologic factor in these obstructions; precipitation should therefore be prevented so far as possible by the administration of adequate fluids and maintenance of an alkaline urine.

In this series of 14 cases, we have encountered a variety of renal changes due to the toxic effects of sulfonamide drugs on the renal parenchyma. In some instances the damage was the essential cause of death, while in others it was of a character serious enough to influence the course of the primary disease toward a fatal termination. Our observations substantiate the general impression that a diminishing output of urine in a patient taking any of the sulfonamide compounds is fair warning that renal injury has set in and that the use of the drug should be stopped promptly and restorative therapy started at once. The corollary to this impression has been that a diminishing oliguria and a satisfactory diuresis are sufficient evidence that the renal damage has been overcome and that a favorable outcome is forthcoming. This has met with contradiction in the work of Luetscher and Blackman.[5] They pointed out that in certain cases of damage to the kidneys by sulfonamide compounds diuresis may develop with a return to normal of the nonprotein nitrogen of the blood but that the patient fails to recover. This is attributed to an excessive volume of urine without adequate excretion of salt. It is emphasized that the failure to replace this lost (saltless) water may lead to unfavorable consequences. Such a specific functional disturbance suggests, according to them, a corresponding specific renal lesion, which they found in the kidneys of 2 of their patients. The possible site of the specific renal injury was given

4. (*a*) Antopol, W., and Robinson, H. J.: Pathologic and Histologic Changes Following Oral Administration of Sulfapyridine, Arch. Path. **29**:67-76 (Jan.) 1940. (*b*) Knoll, A. F., and Cooper, F. B.: Clinical Urolithiasis Medicamentosa Due to Sulfathiazole, Urol. & Cutan. Rev. **44**:292-294 (May) 1940. (*c*) Snapper, I.; Liu, S. H.; Chung, H. L.; Yü, T. F., and Sun, H. M.: Hematuria Renal Colic and Acetylsulfapyridine Stone Formation Associated with Sulfapyridine Therapy, Chinese M. J. **56**:1-10 (July) 1939. (*d*) Pepper, D. S., and Horack, H. M.: Crystalline Concretions in Renal Tubules Following Sulfathiazole Therapy: Widely Patent Foramen Ovale in Patient Aged 77, Am. J. M. Sc. **199**:674-679 (May) 1940. (*e*) Gross, P.; Cooper, F. B., and Scott, R. E.: Urolithiasis Medicamentosa, Urol. & Cutan. Rev. **44**:205-209 (April) 1940. (*f*) Prien, E. L.; Crabtree, E. G., and Frondel, C.: Mechanism of Urinary Tract Obstruction in Sulfathiazole Therapy: Identification of Crystals in Tissue by Polarized Light, J. Urol. **46**:1020-1032 (Nov.) 1941. (*g*) Loewenberg, S. A.; Sloane, N. G., and Chodoff, P.: Sulfathiazole Urinary Calculi in the Kidneys, Ureters and Bladder in the Absence of Marked Urinary Changes Following Sulfathiazole Therapy, J. A. M. A. **115**:2069-2071 (Dec. 14) 1940. (*h*) Reinhold, J. G.; Flippin, H. F., and Schwartz, L.: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, Am. J. M. Sc. **199**:393-401 (March) 1940. (*i*) Thompson, G. J.; Herrell, W. E., and Brown, A. E.: Anuria After Sulfadiazine Therapy, Proc. Staff Meet., Mayo Clin. **16**:609-612 (Sept. 24) 1941. (*j*) Schulte, J. W.; Shidler, F. P., and Niebauer, J. J.: Acute Urinary Suppression Following Sulfadiazine Therapy, J. A. M. A. **119**:411-413 (May 30) 1942. (*k*) Keitzer, W. A., and Campbell, J. A.: Renal Complications of Sulfadiazine, ibid. **119**:701-703 (June 27) 1942. (*l*) Hall, W. H., and Spink, W. W.: Sulfamerazine: Clinical Evaluation in One Hundred and Sixteen Cases, ibid. **123**:126-131 (Sept. 18) 1943. (*m*) Winsor and Burch.[10] (*n*) Bradford and Shaffer.[11] (*o*) Jeck and Orkin.[13]

5. Luetscher, J. A., Jr., and Blackman, S. S., Jr.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration, Ann. Int. Med. **18**:741-756 (May) 1943.

as the intercalated segments of the distal convoluted tubules, the spiral portions of the proximal convoluted tubules and the ascending limb of Henle's loop. These authors added that in all of their cases it was not possible to correlate the retention of salt with the specific renal injury. However, their suggestion that every patient with oliguria due to a sulfonamide compound should be observed and treated with the electrolyte concentration of the blood in mind seems to us a valuable one. Although we did not study this group of patients with the hyperchloremic syndrome in mind, the occasional determinations done revealed that hyperchloremia existed in 1 case.

procedure brings relief is not entirely clear, but it may be possible that by reducing intranephric tension it helps restore normal renal function.

It has been shown experimentally and in man that the sulfonamide compounds may depress renal function. The literature also brings out that these drugs may go further and actually produce morphologic alterations of the renal tissue.[8] This observation has been confirmed by the experience reported in this study. Simple tubular degeneration is common to all kidneys damaged by sulfonamide compounds regardless of what other change may be present. Advanced tubular degeneration is seen in the more fulminating types of complications.[9] This may be

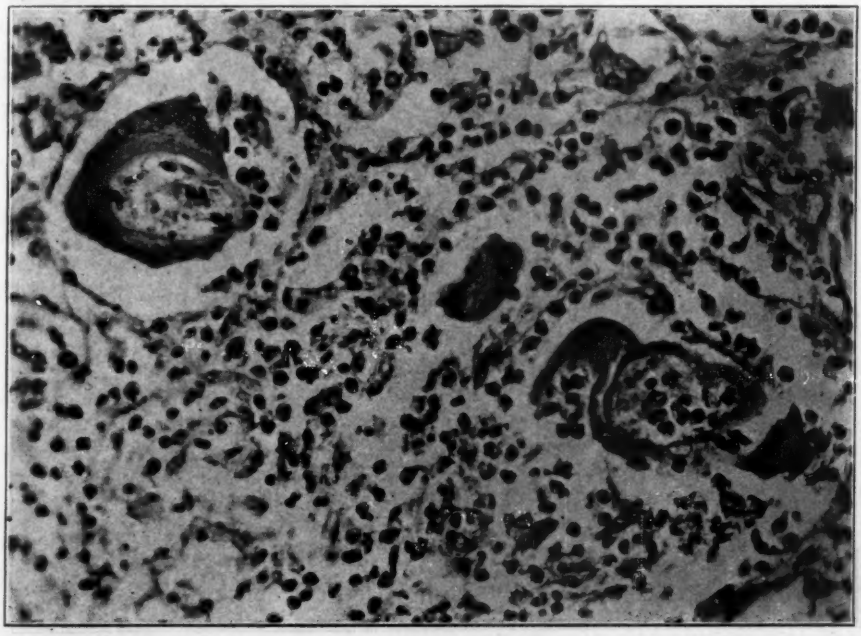


Fig. 5.—Cellular reaction showing the perivascular distribution of some of the giant cells. These are irregular multinucleated giant cells closely applied about the disintegrating vessel walls. Hematoxylin and eosin; approximately 350 diameters.

Decapsulation of the kidney has been advised for the treatment of resistant anuria due to intoxication with a sulfonamide compound. This operation was performed in 1 of our cases, with splendid results. Two other cases have been reported in the literature by Weinstein and Adams[6] and Wattenberg and Coleman.[7] Decapsulation in both of the cases was followed by favorable results. The mechanism by which this

6. Weinstein, M. L., and Adams, E. L.: Sulfathiazole Anuria Cured by Decapsulation of the Kidneys, Am. J. Surg. **60**:105-111 (April) 1943.

7. Wattenberg, C. A., and Coleman, R. C., Jr.: Sulfathiazole Toxic Nephrosis and Kidney Decapsulation, Surgery **14**:570-573 (Oct.) 1943.

8. (*a*) Finland, M.; Strauss, E., and Peterson, O. L.: Sulfadiazine: Therapeutic Evaluation and Toxic Effects on 446 Patients. J. A. M. A. **116**:2641-2647 (June 14) 1941. (*b*) Ravid, J. M., and Chesner, C.: Fatal Case of Hemolytic Anemia and Nephrotic Uremia Following Sulfapyridine Administration, Am. J. M. Sc. **199**: 380-385 (March) 1940. (*c*) Rake, G.; van Dyke, H. B., and Corwin, W. C.: Pathologic Changes Following Prolonged Administration of Sulfathiazole and Sulfapyridine, ibid. **200**:353-362 (Sept.) 1940. (*d*) Merkel and Crawford.[1b] (*e*) Winsor and Burch.[1d] (*f*) Cutts, Burgess and Chafee.[1e] (*g*) Finland, Peterson and Goodwin.[1f] (*h*) Tragerman and Goto.[1g] (*i*) Eggleston and Weiss.[1h] (*j*) Bradford and Shaffer.[1i] (*k*) Erganian and Doval.[2a]. (*l*) Hellwig and Reed. [2b] (*m*) Prien, Crabtree and Frondel.[4f]

(Footnotes continued on next page)

seen in conjunction with interstitial tissue reaction and necrosis. Since the sulfonamide drugs are actually toxic substances, it is not surprising that the tubular system of the kidney may be damaged. This is the usual expression of damage such as that brought about by poisoning with mercury. In some instances, however, there is not only degeneration but an active tissue reaction to the drug, exhibiting an intense inflammatory type of response. This is exemplified by our second case report. The reaction in such cases is probably an expression of severe idiosyncrasy on the part of the renal tissue to the drug. This is an important consideration in the observation of the inflammatory response swelling of the glomerular tufts and congestion are the most common.[8c] Case 3, however, presents a far advanced reaction in the glomeruli. The severe swelling of the tufts, the obliteration of Bowman's spaces, the plugging of the tufts by polymorphonuclear cells and the proliferations of epithelial cells which are infiltrated with polymorphonuclear cells brings to mind the many changes of Bright's disease. However, in this case, with a clinical history of cystopyelitis, the histologic changes of intracapillary glomerulosclerosis of diabetes, the presence of plasma cells and eosinophils in the interstitial tissue and the clinical course and the age of the patient point away from the typical picture of Bright's disease.

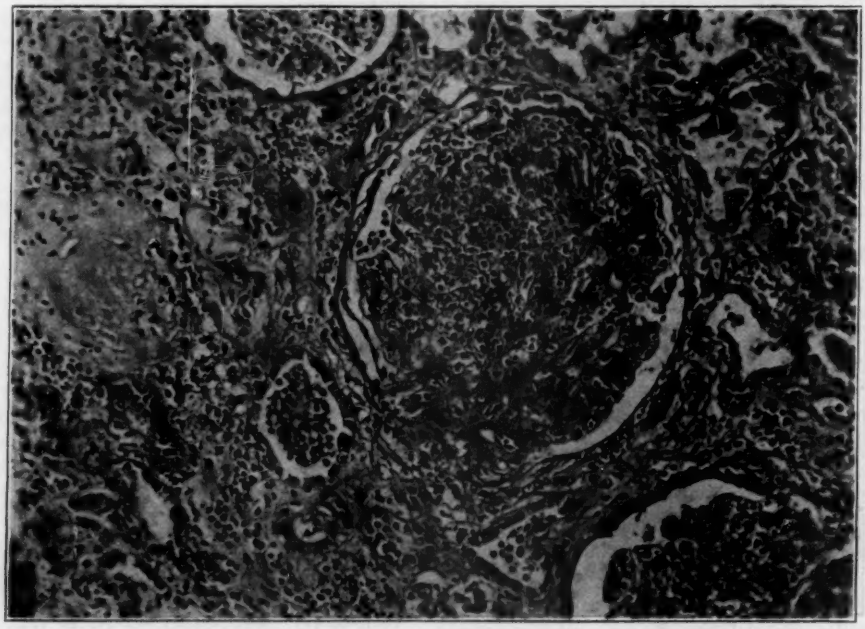


Fig. 6.—Glomerulus showing hyalinized thickening of some of the tufts and diffuse infiltration by polymorphonuclear cells. A loose crescent may be seen infiltrated by polymorphonuclears. Bowman's space is narrow and irregular. Hematoxylin and eosin; approximately 200 diameters.

outside the nephron, such as giant cells and the perivascular distribution of many of the granuloma-like cell accumulations. In this manner it may be true that it is actually an expression which is akin to periarteritis nodosa and other closely related lesions.

Glomerular changes are not encountered as frequently as tubular degeneration. Simple

9. Maisel, B.; McSwain, B., and Glenn, F.: Lesions Produced with Sulfadiazine, Proc. Soc. Exper. Biol. & Med. **49**:715-717 (April) 1942. Cabot Case 28501, New England J. Med. **227**:922-927 (Dec. 10) 1942. Rottino, A., and La Rotonda, O.: A Fatal Case of Urolithiasis Medicamentosa Caused by Sulfadiazine, J. Urol. **48**: 310-317 (Sept.) 1942. Merkel and Crawford.[1b]

On the other hand, it is impossible, in view of these conditions, to attribute all of the glomerular changes solely and unequivocally to the sulfonamide compounds. MacLeod [10] has called attention to the development of an atypical Bright's disease in 2 patients while receiving sulfapyridine for pneumonia. His patients recovered, but he expressed the belief that the drug was the responsible agent for the clinical picture resembling Bright's disease.

This study suggests that a close relationship may exist between hepatic damage and the

10. MacLeod, C. M.: Chemotherapy of Pneumococcic Pneumonia, J. A. M. A. **113**:1405-1410 (Oct. 7) 1939.

nephrotoxic complications. The changes in the liver may be independent of therapy with sulfonamide compounds or may be the result of such therapy. However it may be, closely related hepatotoxic complications due to the sulfonamide compounds are occasionally encountered. Investigation of this is being carried on at present and will be reported at a future date.

SUMMARY

An opportunity presented itself to obtain clinical and pathologic data in 14 cases of renal insufficiency due to intoxication with sulfonamide compounds. Thirteen of the 14 patients died and were studied post mortem. Decapsulation of the kidney was done and a biopsy specimen taken in the case of 1 patient who recovered.

Most of the commonly used sulfonamide compounds were employed but sulfathiazole was the most commonly used one.

The primary disease under treatment was considered to play no part, or at any rate a small role, in causing the renal damage. Although 5 of the 14 patients treated had slight evidence of some renal involvement before therapy was begun, this was not considered a contraindication to the use of sulfonamide compounds, as these drugs have been used successfully in the treatment of acute nephritis.

The quantity of the sulfonamide compound administered and the drug level in the blood appeared to be unimportant in producing the renal damage. As much as 41 Gm. and as little as 10 grains (0.6 Gm.) were responsible for fatal renal injury.

In a few of our cases deposits of crystals of the drugs in the urinary tract causing some degree of mechanical obstruction were found associated with the nephrotoxic lesion; but this was not the rule, as in most of the cases reported the nephrotoxic lesion was independent of mechanical blocking.

Histologically there was simple tubular degeneration present in all the kidneys regardless of what other changes were present. Advanced tubular degeneration, necrosis of the tubular cells and intense inflammatory reaction outside the nephron in the surrounding tissues occurred in some cases. These various tubular lesions undoubtedly represent degrees in the severity of one process rather than different kinds of response. In 1 case advanced changes in the glomeruli are reported.

A correlation between the clinical features and the specific site for the renal tubular damage was not determined in this study.

IMPORTANCE OF BRONCHOGRAPHY IN CASES OF UNRESOLVED PNEUMONIA

CAPTAIN GEORGE S. GRIER III
MEDICAL CORPS, ARMY OF THE UNITED STATES

The frequent demonstration of bronchiectasis by bronchographic studies in cases of unresolved pneumonia[1] has led to this study of 40 patients with bronchiectasis admitted to the station hospital, Fort Eustis, Va., from April 20, 1942 to July 20, 1943.[2]

It is the purpose of this paper not only to show the importance of bronchography in cases of unresolved pneumonia but also to demonstrate that in numerous cases pneumonitis secondary to bronchiectasis is misdiagnosed as primary atypical pneumonia. Atypical, or virus, pneumonia has become a disease of paramount importance in increasing the noneffective rate of military personnel during the past few years.[3] It has been noted at this hospital, both by physical and by roentgen examination, that in the average case atypical pneumonia resolves in about ten days, although the course may be prolonged for several months without any special complications. However, in some cases a condition which on the patient's admission was diagnosed clinically and roentgenographically as atypical pneumonia did not resolve completely and on further study, including bronchography, was found to be pneumonitis around a preexisting bronchiectasis. Ogilvie[4] stated that 36.8 per cent of his series of 68 patients with bronchiectasis demonstrated this syndrome. It is well known that recurrent pneumonitis is the most common complication of bronchiectasis, and any pneumonia which fails to resolve should be suspected of being bronchiectasis.[5] However, pulmonary abscess, pulmonary tuberculosis and cancer of the lung must be considered. Bullowa[6] stated that bronchiectasis with consolidation surrounding the diseased bronchus may be mistaken for primary pneumonia and that pneumonia may be misdiagnosed bronchiectasis. In none of the cases of this series was bronchiectasis thought to be secondary to primary atypical pneumonia.

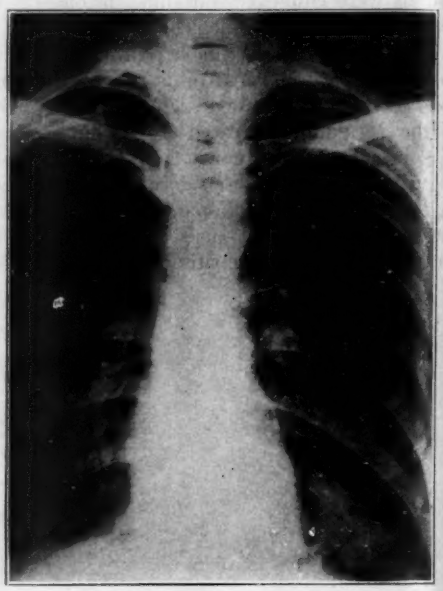


Fig. 1 (case 4).—Flat plate roentgenogram of the chest, showing pneumonitis of the lower lobe of the left lung.

Bronchiectasis stands second only to tuberculosis as the most common chronic disease of the lungs.[7] The routine roentgenograms of the chest of inductees have kept most men with pulmonary tuberculosis from being inducted into the Army, but many men with bronchiectasis are not detected, since a normal roentgenogram

1. Pneumonia in which the pulmonary signs fail to clear up in the usual period.

2. The cooperation of the x-ray department, under Lieutenant T. H. Foust and Lieutenant R. J. Lutz, Medical Corps, Army of the United States, made this study possible.

3. Campbell, T. A.; Strong, P. S.; Grier, G. S., and Lutz, R. J.: Primary Atypical Pneumonia: Report of Two Hundred Cases at Fort Eustis, Virginia, J. A. M. A. **122**:723 (July 10) 1943.

4. Ogilvie, A. G.: Natural History of Bronchiectasis: Clinical, Roentgenologic and Pathologic Study, Arch. Int. Med. **68**:395 (Sept.) 1941.

5. Lisa, J. R., and Rosenblatt, M. B.: Bronchiectasis, New York, Oxford University Press, 1943.

6. Bullowa, J. G. M.: The Management of the Pneumonias, New York, Oxford University Press, 1939.

7. Norris, G. W., and Landis, H. R. M.: Diseases of the Chest, Philadelphia, W. B. Saunders Company, 1938.

of the chest does not exclude bronchiectasis.[8] Patient 30 had a normal roentgenogram of the chest, but extensive saccular bronchiectasis was revealed by bronchographic study with iodized poppyseed oil (fig. 4).

In this series of 40 patients, 9 were referred to the clinic for persons with diseases of the chest because of a history of chronic cough, hemoptysis or recurrent colds in the chest, while the remainder were admitted to the hospital with an initial diagnosis of primary atypical pneumonia.

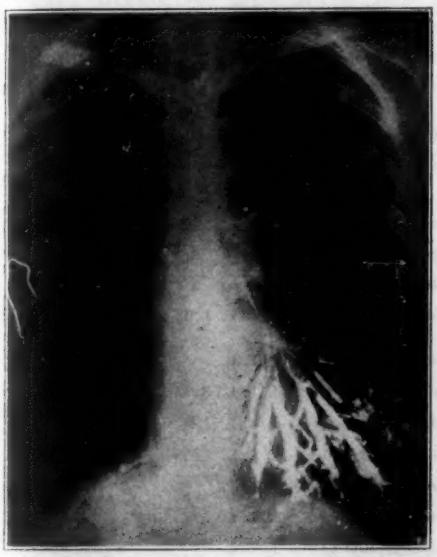


Fig. 2 (case 8).—Tubular bronchiectasis of the lower lobe of the left lung.

The symptoms on admission, in order of frequency, were cough, mucopurulent sputum with occasional blood streaking, substernal soreness, chills, fever and sweats. Examination revealed slight impairment of resonance, suppressed breath sounds, and fine, crackling and coarse rales in the lower lobe of one or both lungs. White blood cell counts showed slight leukocytosis but little increase in the polymorphonuclear neutrophils. The sputum did not settle into three layers in any case, and no organisms predominated, but those present were usually in the gram-positive coccus group. Clubbing of the fingers was not seen in any patient, although several men had long-standing symptoms and extensive disease. Roentgenograms demonstrated stringy and mottled densities in the lower lobes of the lungs, usually unilateral and radiating out from the hilus toward the diaphragm (fig. 1). Lateral roentgenograms of the chest frequently revealed a pneumonic process behind the diaphragm or a cardiac shadow which could not be seen in the posterior-anterior exposure.

After four or five days the acute febrile stage usually subsided and the cough abated somewhat, with less sputum, while suppressed breath sounds and rales persisted or improved slightly. Follow-up roentgenograms of the chest were taken at seven to ten day intervals and showed little evidence of clearing.

Bronchographic studies were done in cases in which resolution failed to occur in four to six weeks, and iodized poppyseed oil was injected into both sides even when the pneumonic process was unilateral. Studies with iodized oil are contraindicated in the period of acute pneumonitis, since this procedure may produce an exacerbation of the acute process.

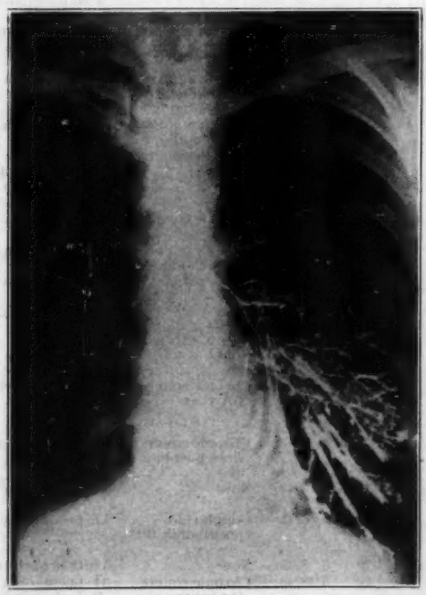


Fig. 3 (case 4).—Fusiform and tubular bronchiectasis of the lower lobe of the left lung.

TECHNIC OF BRONCHOGRAPHY

In preparation for the bronchographic study, the patient takes nothing by mouth after breakfast. At 11 a. m. he is given 3 grains (0.18 Gm.) of sodium amytal. At 1:30 p. m. ⅙ grain (0.01 Gm.) of morphine sulfate and $\frac{1}{150}$ grain (0.4 mg.) of atropine sulfate are administered. Local anesthesia is induced with cocaine hydrochloride, a 2 per cent solution being sprayed into the pharynx and a 10 per cent solution being injected into the larynx with a laryngeal cannula. The

8. Hedblom, C. A.: Surg., Gynec. & Obst. **52**:406, 1931.

Case	Age	Date of Bronchogram	Past History of Diseases of Chest	Diagnosis on Admission	Type of Bronchiectasis	Extent	Location	Comments
1. J. M.	27	4/20/42	None	At. pneumonia R. L. L.	Fusiform	Moderate	R. L. L., R. M. L.	
2. W. M.	33	4/21/42	Chronic cough; pneumonia 1926	Bronchiectasis	Fusiform	Moderate	R. M. L., L. L. L.	
3. A. R.	27	4/27/42	Chronic cough	At. pneumonia L. L. L.	Fusiform	Moderate	L. L. L.	
4. J. C.	28	4/28/42	None	At. pneumonia L. L. L., R. U. L.	Fusiform	Extensive	L. L. L.	
5. H. W.	36	7/ 1/42	Chronic cough	Bronchiectasis	Saccular	Moderate	L. L. L.	
6. J. D.	26	7/ 7/42	Pneumonia 10 yr. ago	At. pneumonia L. L. L.	Fusiform	Moderate	L. L. L.	
7. W. K.	37	8/15/42	None	At. pneumonia R. L. L., L. L. L.	Fusiform	Mild	R. L. L., L. L. L.	
8. G. W.	25	8/18/42	Worked in soapstone dust; cough 2 mo.	Bronchiectasis	Tubular	Moderate	L. L. L.	Pneumoconiosis; patient admitted after severe hemoptysis
9. W. M.	28	8/21/42	Chronic cough	Bronchial asthma	Tubular	Moderate	L. L. L.	
10. C. S.	40	8/26/42	None	At. pneumonia R. L. L.	Saccular	Moderate	R. L. L.	
11. G. T.	27	8/31/42	Chronic cough for years	Bronchiectasis	Tubular	Moderate	L. L. L.	Dementia precox
12. J. M.	31	9/25/42	Chronic cough 2 yr., worse in past 2 mo.	At. pneumonia L. L. L.	Fusiform	Mild	L. L. L.	Secondary anemia
13. D. D.	24	9/29/42	None	At. pneumonia R. L. L.	Fusiform	Moderate	R. L. L., L. L. L.	
14. C. S.	25	10/ 1/42	Pneumonia 5 yr. ago; chronic cough	Bronchiectasis	Fusiform	Moderate	R. L. L., L. L. L.	Loss of weight; postnasal drip for 1 yr.; secondary anemia
15. W. G.	35	10/30/42	Chronic cough	Bronchiectasis with pneumonitis	Fusiform	Mild	L. L. L.	Abscessed teeth
16. J. S.	44	11/12/42	Chronic cough 15 yr.	Bronchiectasis with pneumonitis	Tubular	Mild	L. L. L.	Frequent hemoptysis; profuse sputum
17. W. B.	21	11/18/42	None	At. pneumonia L. L. L.	Tubular	Extensive	L. L. L.	
18. G. J.	20	11/27/42	Pneumonia twice in childhood; chronic cough	At. pneumonia L. L. L.	Fusiform	Moderate	R. L. L., L. L. L.	Frequent colds in chest
19. W. P.	34	11/27/42	Pneumonia in childhood	At. pneumonia bilateral	Tubular	Moderate	L. L. L.	
20. A. P.	40	11/28/42	Chronic cough	Bronchiectasis with pneumonitis	Saccular	Extensive	L. L. L., R. L. L.	
21. H. S.	20	1/ 6/43	None	At. pneumonia L. L. L.	Tubular	Extensive	L. L. L.	
22. J. R.	20	3/ 3/43	Chronic cough	At. pneumonia L. L. L.	Tubular	Extensive	L. L. L.	
23. C. S.	27	3/17/43	Chronic cough since childhood	At. pneumonia L. L. L.	Tubular	Moderate	L. L. L.	Postnasal drip for 20 yr.
24. P. G.	28	3/18/43	None	At. pneumonia R. L. L.	Tubular	Localized	R. L. L.	
25. A. G.	34	4/ 5/43 5/12/43	None	At. pneumonia; atelectasis	Tubular	Mild	L. L. L.	Second bronchogram showed improvement
26. J. H.	29	3/23/43	None	At. pneumonia L. L. L.	Tubular	Moderate	L. L. L.	
27. S. W.	32	4/ 9/43	Chronic cough for years	Chronic bronchitis	Fusiform	Localized	L. L. L.	Second bronchogram 2 mo. later showed improvement
28. R. C.	18	4/23/43	Chronic cough since pneumonia at 4	Lobar pneumonia	Saccular	Extensive	R. L. L.	Prolonged convalescence from pneumonitis
29. G. L.	18	5/ 3/43	None	At. pneumonia	Fusiform	Mild	R. L. L.	Persistent signs of consolidation
30. C. H.	19	5/ 6/43	Cough since pneumonia 1941	At. pneumonia	Saccular	Extensive	R. L. L.	Marked puddling effect on bronchogram
31. A. T.	20	5/ 8/43	None	Acute bronchitis	Tubular	Mild	R. L. L.	
32. D. H.	20	5/18/43	Chronic cough for years	At. pneumonia R. L. L.	Tubular	Moderate	R. M. L., R. L. L.	
33. C. M.	21	5/22/43	None	At. pneumonia R. M. L.	Tubular	Moderate	R. M. L.	
34. C. S.	31	5/28/43	Chronic cough; bronchopneumonia 2 yr. ago	Bronchiectasis	Saccular	Localized	R. L. L.	Frequent colds in chest and hemoptysis
35. C. S.	20	6/ 3/43	None	At. pneumonia R. L. L., R. M. L.	Fusiform	Extensive	R. M. L., R. L. L.	
36. E. M.	21	6/10/43	Cough since pneumonia 1942	At. pneumonia R. L. L.	Tubular	Moderate	R. M. L., R. L. L.	
37. R. G.	19	6/11/43	Frequent chest colds since childhood	At. pneumonia R. L. L.	Tubular	Moderate	R. L. L.	
38. W. L.	27	6/23/43	Chronic cough since pneumonia ("flu") 1933	At. pneumonia L. L. L.	Tubular	Extensive	L. L. L.	
39. E. T.	19	7/ 1/43	Chronic cough 2 yr.	At. pneumonia	Fusiform	Localized	R. M. L.	
40. R. M.	19	7/20/43	Chronic cough since pneumonia 1942	At. pneumonia L. L. L., R. L. L.	Tubular	Moderate	L. L. L.	

actual bronchographic examination is then carried out as follows:

1. Using a soft rubber catheter, place the tip in the piriform sinus as shown under fluoroscopic examination in the lateral view.

2. Inject iodized poppyseed oil after the patient has been placed in the desired position to outline a specific lobe.

3. Under fluoroscopic control note well the flow of the oil through the bronchi out into the alveolar spaces.

4. Take stereoscopic anterior-posterior and oblique films when both sides are outlined. If

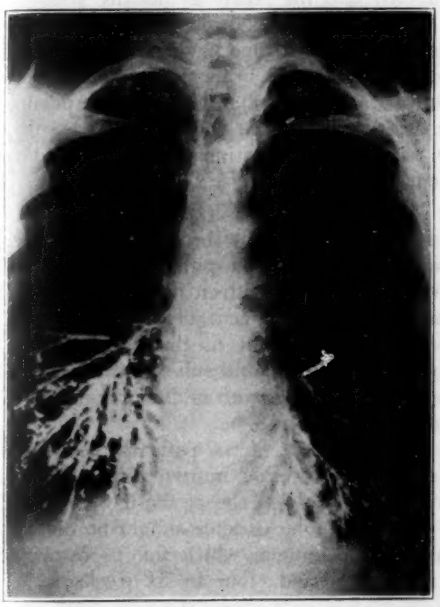


Fig. 4 (case 30).—Saccular bronchiectasis of the lower lobe of the right lung, with a puddling effect. The bronchogram of the lower lobe of the left lung is normal.

one side is being studied a lateral may be substituted for the oblique view.

Postural drainage should be instituted after the patient returns to the ward.

Although the age group was limited, it was found that the average age was 26½ years and that 17 patients were under 25 years, 17 between 25 and 35 and 6 over 35.

SUMMARY OF CLINICAL DATA

In summarizing the statistical data (presented in the accompanying table) it is found that the distribution of bronchiectasis was usually unilateral (30 cases) and most frequently involved the lower lobe of the left lung (20 cases; 50 per cent). The preponderance of left-sided disease in instances of unilateral bronchiectasis is in accord with Ogilvie's [4] series. The lower lobe of the right lung was occasionally affected alone (8 cases; 20 per cent), while the middle lobe of the right lung rarely demonstrated the disease by itself (2 cases; 5 per cent). Bilateral distribution was noted in 6 cases (15 per cent); in 5 of these the lobes of both lungs were involved, while in the remaining case the middle lobe of the right lung and the lower lobe of the left were affected. In 4 cases (10 per cent) the diseased bronchi were limited to the middle and lower lobes of the right lung together. Farrell's [9] figures in 100 cases showed involvement of the left lung in 41 per cent, of the right lung in 23 per cent and of both lungs in 36 per cent. Fletcher [10] found a similar distribution in 100 cases, with the left lung involved in 43 per cent, the right lung in 25 per cent and both lungs in 32 per cent. It is interesting to note that none of the patients in whom disease of upper

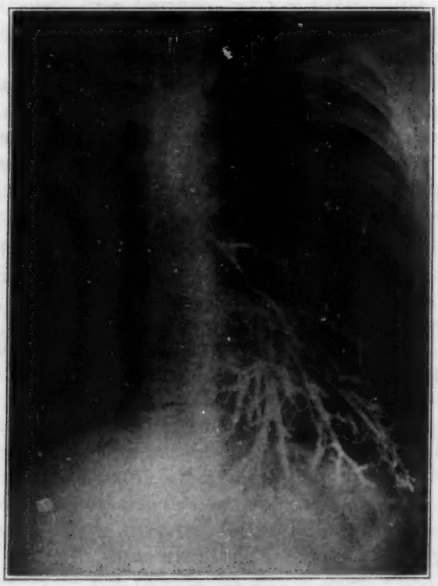


Fig. 5.—Bronchogram showing blunting of the bronchi and absence of alveolar filling, with no evidence of dilatation of the bronchi. This patient had some atelectasis of the lower lobe of the left lung.

lobes was suspected could be demonstrated to have bronchiectasis in the upper lobes.

Tubular (19 cases) and fusiform (15 cases) dilatations were the most frequent type of

9. Farrell, J. T., Jr.: Importance of Early Diagnosis in Bronchiectasis: Clinical and Roentgenologic Study of One Hundred Cases, J. A. M. A. **106**:92 (Jan. 11) 1936.

10. Fletcher, E. J.: J. Thoracic Surg. **4**:461, 1935.

bronchiectasis demonstrated, while the saccular form (6 cases) was seen rather infrequently (figs. 2, 3 and 4).

According to Lisa and Rosenblatt [5] the size and extent of the dilatations have no direct relation to the severity of the disease. However, it is of interest to note that 9 patients in this series showed extensive bronchiectasis, 20 moderately severe and 7 mild, and only 4 had localized disease.

In 2 cases not included in this series a diagnosis of primary atypical pneumonia was made on the patient's admission and the course of the disease was similar to that described in this study. Bronchographic studies did not show dilatation of the bronchi but demonstrated atelectasis, as shown by absence of alveolar filling, blunting and crowding together of the bronchi (fig. 5). Follow-up studies with iodized oil in six weeks revealed complete aeration of the atelectatic areas and normal bronchial trees. These 2 cases are mentioned because atelectasis without bronchial dilatation must not be confused with atelectatic bronchiectasis, since the former is reversible while the latter usually is not.[4]

Brennemann [11] stated that early diagnosis of atelectasis as a prebronchiectatic condition is important and that the condition can be cured by removal of the obstruction and bronchoscopic aspiration.

COMMENT

It has been found in this study that the differential diagnosis between primary atypical pneumonia and pneumonitis around bronchiectasis is difficult at the onset. A history of chronic cough, especially following bronchopneumonia in childhood, hemoptysis, profuse sputum or frequent colds in the chest makes one suspicious of bronchiestasis, although in some cases the past history may be entirely without such elements. In the series under study, only 23 patients gave a history of chronic cough, and in 9 of these patients the cough developed after a previous attack of pneumonia.

The frequent diagnosis of this disease is brought out by the fact that during the fifteen months in which this study was made there was an average of 2.66 cases a month. This is significant when one considers that the patients were inducted into the Army as healthy young men.

The importance of bronchography in cases of unresolved pneumonia is demonstrated by the fact that 31 of 40 bronchiectatic patients were admitted to the hospital with an acute pneumonic process which did not show clearing by physical or roentgen examination after prolonged treatment.

SUMMARY AND CONCLUSIONS

Forty patients with bronchiectasis were admitted to the station hospital at Fort Eustis, Va., during a period of fifteen months. Sixty-seven and five-tenths per cent of the patients in this series had an initial misdiagnosis of primary atypical pneumonia and subsequently were found to have pneumonitis around a preexisting bronchiectasis.

In 75 per cent of the patients the bronchiectasis was unilateral; in two thirds of these it involved the lower lobe of the left lung.

Bronchographic studies should be done in all cases of pneumonia which fail to resolve in a reasonable period (four to six weeks).

11. Brennemann, J.: Dis. of Chest **9**:39, 1943.

INFECTIOUS MONONUCLEOSIS

A STUDY OF ONE HUNDRED AND NINETY-SIX CASES

ANDREW W. CONTRATTO, M.D.

CAMBRIDGE, MASS.

Infectious mononucleosis, also called glandular fever, presents a problem in diagnosis to physicians, especially those attending large groups of young people. Although it is well known that any young febrile adult suffering with symptoms of a more or less simple sort (cold, sore throat, grip, etc.) should be suspected of having infectious mononucleosis and the necessary laboratory tests made to determine the fact definitely, the procedures are often overlooked. At the Stillman Infirmary, connected with Harvard University, my colleagues and I have observed and attended a large number of young men suffering from this disease. I believe that this is the largest series yet reported and made available for study. From 1935 up to and including June 1943 there were 12,601 men admitted to the Stillman Infirmary for medical care, of whom 249 had a discharge diagnosis of infectious mononucleosis. Of this number, 53 were eliminated as not presenting a typical enough picture of the disease to have their cases included in this study. The cases of the remaining 196 patients are the basis for the material presented here.

This group of 196 patients is 1.5 per cent of the total number of medical admissions—a high incidence when compared with the figures in general hospitals.

At the Peter Bent Brigham Hospital, in Boston, there were 16,907 medical admissions from September 1935 to June 1943. Of this number a diagnosis of infectious mononucleosis was made for only 61 persons, a sharp contrast with the figures from the infirmary.

Spark [1] stated that in the Sydney Hospital, Australia, there had been but 9 inpatients with a diagnosis of infectious mononucleosis, or glandular fever, in the last twenty-two years and in the Royal Prince Albert Hospital but 7 such patients in thirty-two years; at the Royal Alexander Hospital for Children, he was unable to find any inpatient with this diagnosis. Spark expressed the belief that this small number was due largely to the lack of an accurate diagnosis, as it was not until 1934 that there were any cases of infectious mononucleosis reported in these institutions.

Longcope [2] reported 10 cases which he had gathered from 1909 to 1922 and made the statement that the "disease has been mistaken for tuberculosis, typhoid fever, Hodgkin's disease, and leukemia."

The reasons for the discrepancy between the number of diagnoses of this disease in a college infirmary and in a general hospital are that my series dates only from 1935 and the recognition of infectious mononucleosis is recently more common. Also, a general hospital admits persons of all ages, and infectious mononucleosis is a disease with a special affinity for the young, although Moir [3] reported the case of a patient of 70. In addition, many patients with infectious mononucleosis do not feel ill enough to see a physician, much less be admitted to a general hospital. The students at Harvard University usually do not escape the eye of a physician, as it is a rule that an ill student must report to the department of hygiene and in this way even a mild indisposition is discovered.

The problem of diagnosis in infectious mononucleosis cannot be overemphasized, especially from the point of view of a college infirmary, where many students are far from home and anxious parents are apt to write or telegraph and otherwise seek accurate information. Because the typical blood changes and laboratory criteria for making this diagnosis certain may not appear for many days after the onset of the symptoms, it is naturally unwise without this information to characterize the disease by name, even though one is suspicious of its presence. The variability of the symptoms and physical manifestations with accompanying complications combine to make this illness a diagnostic problem; and, although recent knowledge and interest in the subject have greatly assisted in eliminating some of the difficulties, it is not understood well enough to rule out at all times rather serious diagnostic pro-

From the Department of Hygiene, Harvard University.

1. Spark, T. E. H.: Infectious Mononucleosis: A Problem in Diagnosis, M. J. Australia **2**:413, 1942.

2. Longcope, W. T.: Infectious Mononucleosis (Glandular Fever) with a Report of Ten Cases, Am. J. M. Sc. **164**:781, 1922.

3. Moir, J. I.: Glandular Fever in the Falkland Islands, Brit. M. J. **2**:822, 1930.

cedures. However, too frequently patients have had to endure excision of lymph nodes, sternal puncture or blood transfusion before infectious mononucleosis was suspected and simple laboratory procedures made the diagnosis certain. Extended fatigue and general malaise, which is a common feature of this disease, may excite the patient or his family with the thought of a lingering illness.

Bernstein,[4] discussing 66 cases, has given the most complete and comprehensive report on this subject to date, with a review of the literature which includes 207 references. In this excellent paper, he has described in great detail many of the difficulties which I have only touched on at this point. His thorough observations and description of the symptomatology, clinical manifestations and laboratory data have been a source of great assistance in the preparation of this paper.

Infectious mononucleosis is benign for the most part, but because of the variability of complaints before the onset, the variability of the initial symptoms, the many and varied physical signs and complications of both a mild and seemingly alarming character during the course of the illness, it was felt that the series at the Stillman Infirmary afforded important detailed information of a clinical nature which should be presented for practical purposes in the study of infectious mononucleosis. No attempt has been made to survey the literature on this subject completely nor to present laboratory data or research material past and present. The purpose of the paper is to present observations on a large group of patients whose final clinical diagnosis of infectious mononucleosis has been as accurate as it was possible to make and with as much clinical evidence as I have collected to demonstrate the extreme variability of the disease in all its stages, in the hope that some of the diagnostic problems may be clarified.

INCIDENCE

The patients discussed in this study were all students of Harvard University with an average age of 20 years, the youngest being 17 and the oldest 26. The study covers an eight year period of admissions to the Stillman Infirmary, from the fall of 1935 to June 1943. The diagnosis of infectious mononucleosis was made in 249 instances, but in a critical survey of the case histories 53 were excluded because of a negative result of a heterophile test or a blood smear that was not considered typical. Undoubtedly some of these persons whose cases were excluded were suffering with infectious mononucleosis, and a more complete study would have enabled my colleagues and me to make a certain diagnosis.

Although some authors feel that the disease is more prevalent during certain seasons or months of the year, this has not been borne out by this study (table 1). Inasmuch as the infirmary was not open during the summer months, with the exception of the summer of 1942, the incidence would be much less in this season. Also, the Christmas holidays, of at least ten days to two weeks, would account for the lower number of cases during December.

Epidemics of infectious mononucleosis have been reported by several authors,[5] but I have had no reason to suspect that the disease is highly contagious. The discrepancy in the number of cases from year to year (table 1) is in my opinion due to the fact that the diagnosis was made more frequently when the visiting

TABLE 1.—*Incidence of Infectious Mononucleosis*

Yearly Totals		Monthly Totals 1935-1943	
1935-1936	9	January	21
1936-1937	18	February	27
		March	22
1937-1938	18	April	23
		May	29
1938-1939	26	June	10 (partial vacation)
1939-1940	26	July	vacation
		August	vacation
1940-1941	33	September	12 (partial vacation)
1941-1942	44	October	34
		November	9
1942-1943	22	December	9 (partial vacation)
Total	196	Total	196

personnel of the infirmary suspected the illness and made the necessary tests to prove it. Also, the amount of general illness varies considerably from year to year in the infirmary, the total number of admissions in one year being 1,500 and in another, 2,200. Therefore, I feel that the scale in numbers is not indicative of epidemic proportions in our study. No special precautions were used in the handling of these patients, and they were admitted to an open ward. To my knowledge, there was no instance in which a patient in an open ward has contracted the disease from another patient. Also, no case was reported of one roommate's contracting the disease from another, although the patient may have

4. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85, 1940.

5. (*a*) Pfeiffer, E.: Drusenfieber, Jahrb. f. Kinderh. **29**:257, 1889. (*b*) Guthrie, C. C., and Pessel, J. F.: An Epidemic of "Glandular Fever" in a Preparatory School for Boys, Am. J. Dis. Child. **29**:492 (April) 1925. (*c*) Moncrieff, A.: Two Cases of Glandular Fever in a Family, Lancet **1**:883, 1932. (*d*) Nolan, R. A.: Report of So-Called Epidemic of Glandular Fever (Infectious Mononucleosis), U. S. Nav. M. Bull. **33**:479, 1935. (*e*) West, J. P.: An Epidemic of Glandular Fever, Arch. Pediat. **13**:889, 1896.

been ill for several days before being admitted to the infirmary. This experience is different from that which one encounters when dealing with diseases which are obviously highly contagious, such as measles, German measles, chickenpox and mumps.

SYMPTOMATOLOGY

One of the most striking features of infectious mononucleosis is the wide variability in the type and severity of its symptomatology. Several of the patients in this series were thought to be neurotic because of their continuous complaints of extended fatigue and malaise although the general physical examination showed nothing abnormal and there was no elevation of temperature. The accurate diagnosis was made only after a blood count and smear proved to be typical of this disease. On the other hand, in contrast to this mild onset, many of the patients were prostrated, with high fever, resembling the picture of typhoid or severe streptococcic infection of the throat. Between these two extremes is the great majority, with such a wide variability of symptoms and physical signs that unless adequate thought had been given to infectious mononucleosis the diagnosis would have gone into the general category of infections of the upper respiratory tract.

Sore throat was undoubtedly the most common symptom of which these patients complained. Although it did not occur as the presenting symptom in more than 50 per cent of the cases, it developed at some time during the course of the illness, so that all except 35, or 18 per cent, of the patients had this complaint at some time during the infection. The degree of sore throat was variable, being of a mild nature in some, described as merely "dry," while in others it was so severe as to cause pain when the patient was swallowing liquid.

Headache often heralded the onset of the disease, being so mild in some cases that little attention was given to it while in others it was extremely severe, of enough concern to the physician to make him question whether he might be dealing with typhoid or spinal meningitis.

Fatigue and general malaise were both frequent companions to other symptoms, often preceding the more acute onset of the illness by some days or even a week or two.

Gastrointestinal symptoms were not particularly prevalent, and, with the exception of patients in whom jaundice, nausea and vomiting later developed, it occurred very infrequently. Pfeiffer [5a] and Bernstein [4] both mentioned that the frequency of constipation is striking, but it was present in only a few of these patients. It seemed worthy of little consideration as a symptom of the disease, since any active patient confined to bed may become constipated. Diarrhea also was an infrequent symptom; the only case in which it was serious is discussed in the paragraph on complications. Abdominal pain was present in only a few instances in this series and was usually accompanied by diarrhea. A report of 1 case in which abdominal pain was indicative of a condition in the abdomen requiring surgical treatment is also discussed in the paragraph on complications. In this case, an acutely diseased appendix was removed. This example contrasts sharply to abdominal pain and the sequelae as described by Davidsohn,[6] who, in his experience, never found a typical acutely inflamed appendix when operation was performed but found what he felt to be a condition due to a direct complication of infectious mononucleosis.

Anorexia was a common symptom, its degree and duration depending largely on the severity of other symptoms accompanying the illness.

A presenting symptom of stiff or sore neck was usually referable to the swollen cervical lymph nodes. The onset of the lymphadenopathy was usually found in this area and, for some unknown reason, often on the left side.

The symptoms of ordinary infections of the upper respiratory tract, with nasal congestion, fever and chills, were conspicuous. However, true chills occurred infrequently, and when they did occur they were accompanied by high temperatures. Generalized aches and pains such as one would associate with "grip" were often present. Pain on moving the eyeballs was mentioned by several in describing their initial symptoms. Cough, a mild presenting symptom, was noticed subjectively by 11 patients. Sweating and dizziness were seen only occasionally.

In table 2 are listed all the presenting symptoms as a single complaint and also combined with two or more symptoms. It will be noted that a great number of patients had more than one symptom but also that a considerable number complained of only one symptom at the time of admission, sore throat being the most frequent.

PHYSICAL SIGNS

Inflammation of the Throat.—Sore throat is the outstanding subjective symptom of infectious mononucleosis. It was the initial symptom of 96, or about 50 per cent, of the patients in this series, many of whom complained of a sore or "dry" throat for days or even weeks preceding the appearance of other symptoms. One hundred

6. Davidsohn, I.: Infectious Mononucleosis, Am. J. Dis. Child. 49:1222 (May) 1935.

and sixty-one, or 82 per cent, complain of a sore throat at some time during the course of the illness.

The objective observations concerning the throat were extremely varied. In 31 patients, the throat was normal in appearance throughout the course of the illness; in 56, it was mildly injected. In 66 the throat was moderately red for several days, and in 43 it showed either pronounced follicular tonsillitis or an ulcerative pharyngitis with sloughing of tissue. When the throat was found to be noticeably injected, it usually remained sore for a week or ten days and was the most annoying symptom, as even the swallowing of water caused pain and discomfort.

Smears from the ulcerated lesions revealed a mixture of streptococci, fusiform bacilli and spirochetes.

in all cases of Vincent's angina to be sure that blood smears and heterophile tests are made to assure an accurate diagnosis.

Fever.—Fever was present in all except 22, or 11 per cent, of the patients in this series. The elevation of the temperature and its duration were variable. The highest fever encountered was 105 F. (in 1 patient only and continuing at that level for three days) and the longest duration of fever was thirty-two days (in just 2 patients). Seventy-seven, or 39 per cent, of the patients had an elevated temperature for less than five days. Thirty-eight patients (19 per cent) had fever from ten to fifteen days, and 27 (13 per cent) had fever of more than fifteen days' duration.

The fever is of the spiking nature and has no definite course. In some cases the high point of the fever was in the morning; in others, at

TABLE 2.—*Presenting Symptoms of Patients with Infectious Mononucleosis*

		Combination of Two Presenting Symptoms														Combination of Two or More Symptoms	Grand Total
Single Chief Complaint	No.	Sore Throat	Fatigue	Headache	Cold	Fever	Enlarged Nodes	General Aches and Pains	Gastrointestinal Symptoms	Chills	Soreness of Eyes	Cough	Sweating	Dizziness	Earaches		
Sore throat	33	..	..	4	12	1	8	10	..	..	..	1	..	..	..	27	96
Fatigue	14	..	..	..	..	..	..	..	..	..	..	..	..	..	..	69	83
Headache	6	4	..	..	2	1	1	3	..	..	2	..	..	..	..	25	44
Cold	7	..	..	2	..	1	..	1	..	..	..	..	..	..	..	32	43
Fever	1	1	..	..	1	1	..	5	1	4	..	..	..	..	..	28	42
Glands	4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	35	39
General aches and pains	1	10	..	3	1	5	..	..	..	2	1	..	..	..	..	0	23
Gastrointestinal symptoms	2	..	..	..	..	1	..	..	..	..	..	..	..	1	..	13	17
Chill	0	..	..	..	..	4	..	2	..	..	..	..	..	..	..	5	11
Soreness of eyes	2	..	..	2	..	..	..	1	..	..	..	..	..	..	..	6	11
Cough	0	1	..	..	..	..	..	..	..	..	..	..	..	..	..	10	11
Sweating	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	6	6
Dizziness	1	..	..	..	..	..	..	..	1	..	..	..	..	..	..	2	4
Earache	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	4	4
Totals	71	16	0	11	16	14	9	22	2	6	3	1	0	1	0	262	434

Vincent's Angina.—Tender, bleeding gums, often spongy and swollen and sometimes ulcerated, appeared in 13 patients in this series. In all except 2 of these, this condition was accompanied by a sore throat, usually complicated by ulceration of the tonsillar pillars or the pharyngeal wall. The involvement of the gums frequently preceded the inflammation of the throat and in some cases was more severe. This often led to a diagnosis of Vincent's angina early in the disease, which was later corrected by the heterophile test and blood smear. From this experience, I feel that many patients who display nothing more than bleeding or tender gums, which may be either swollen or spongy or both, may well have infectious mononucleosis. Since this condition may closely simulate a purely local infection or others of a more serious nature, such as pharyngeal diphtheria, it would be wise

noon, and in still others it was in the late afternoon or evening. In a number of cases the temperature would return to normal for a period of twenty-four hours and then would again become elevated for four or five days. The amount of fever and its duration did not seem necessarily related to either the sore throat or the blood count. In many cases in which the sore throat was a minor complaint, the temperature was quite high and remained elevated for many days. There was no direct relationship between the amount of fever and the lymphadenopathy or between the fever and splenomegaly. Several instances were noted in which by the time the lymph nodes became enlarged, the spleen palpable and the blood smear diagnostic the temperature had abated and the patient was feeling much better. In some of the cases in which a diagnosis of neurosis was made during

the early part of the disease because of continued fatigue and a noncontributory physical examination, including a normal temperature, a slight fever may have been present at some time during the twenty-four hours. These men, because of normal results of physical examination and absence of fever at the time they reported to the clinic, were not hospitalized and were forced to carry on their usual routine. It is little wonder that they continued to return to the clinic with the complaint of extreme fatigue and exhaustion.

Lymphadenopathy.—The common conception in the past that enlargement of lymph nodes always accompanies infectious mononucleosis did not prove true in this series. Thirty-two, or 17 per cent, of the patients had no enlargement of peripheral nodes at any time during the course of the illness, although the clinical course, the hemogram and the heterophile examination led to a diagnosis of infectious mononucleosis. Tidy and Daniel [7] stated that infectious mononucleosis with no glandular enlargement is rare and suggested that the patients having no such enlargement must have enlarged mesenteric or mediastinal glands. This, of course, cannot be proved or disproved in a study of this type.

The striking feature of the lymphadenopathy in this series is that in the great majority of cases it did not appear early in the disease. Definitely enlarged superficial lymph nodes were noted in only 19 patients at the time they appeared with their original complaints. Many of the remaining patients acquired enlarged superficial lymph nodes in several days or a week after the onset of illness, but a moderate number had no lymphadenopathy until the other symptoms had abated and they were well on their way to recovery. In several cases no glandular enlargement was noted until two or three weeks after the onset. Landes [8] reported the case of a seriously ill young man who, despite a positive heterophile reaction and a careful daily examination, did not have enlarged nodes until twelve days after he entered the hospital, which was twenty-two days after the onset of the symptoms.

Generalized glandular enlargement was noted in only 10 cases.

It is difficult to state the exact size of the lymph nodes in this illness. Nodes which I considered slightly palpable, might be described as being of the size of a small pea; for glands which I considered moderately palpable, a large pea would be descriptive, and glands which were found to be easily palpable were about the size of a hazelnut. In no instance were the glands found to be extremely large and matted together. I suggest that if such a condition occurs, a diagnosis other than infectious mononucleosis be considered.

Enlargement of the cervical lymph nodes was the most common chain involvement and was present in 149 patients. In 82 of this number they were mildly enlarged; in 57, moderately enlarged, and in 10, easily palpable.

Sixty patients were found to have enlargement of the axillary nodes; in 45 of these they were mildly enlarged; in 14, moderately enlarged, and in 1, easily palpable.

Enlargement of the occipital nodes was noted in only 5 patients.

It is to be observed that in this entire series of 196 patients there was never lymphadenopathy in any other region when cervical nodes were not palpable.

It should be borne in mind that one must differentiate enlargement of the cervical lymph nodes from enlargement of the cervical salivary glands. One of the frequent errors made in diagnosis is the not too careful consideration of this point. Students have frequently been sent to the infirmary with a tentative diagnosis of infectious mononucleosis, when closer examination revealed that they were actually suffering from mumps. Moreover, in all schools and colleges, one frequently encounters epidemics of German measles. It is my opinion that in the great majority of instances German measles is accompanied with the greatest enlargement of the lymph nodes of the occipital and postauricular chains, while in infectious mononucleosis, enlargement of the occipital and postauricular lymph nodes occurs only after one can easily palpate larger anterior cervical or inguinal nodes.

The lymphadenopathy is usually transient and in the majority of cases has completely abated within two or three weeks. In some cases, however, the lymph nodes may remain slightly enlarged for a period of a month or two, but in no case was any notable lymphadenopathy encountered after two months.

Splenomegaly.—The spleen was palpable in 91 patients. Although this is less than half of the number of patients observed, it makes one realize that the palpability depends largely on the examiner; and when one discusses whether or not the spleen is palpable it should be remembered that the differences of opinion of the examiners must be considered.[4] Most of the patients in this study were examined by the same physicians,

7. Tidy, H. L., and Daniel, E. C.: Glandular Fever and Infectious Mononucleosis, with an Account of an Epidemic, Lancet **2**:9, 1923.

8. Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis: Report of a Case, J. A. M. A. **116**:2482 (May 31) 1941.

and an effort was made to feel the spleen daily during the time that the patient was confined to the infirmary and as many patients as possible were seen at regular intervals after they were discharged.

Of the 91 patients with a palpable spleen, 67 had spleens which were barely felt and 15 had spleens which were easily palpable; in 9 instances the spleen was enlarged about 2 fingerbreadths below the left costal margin. In several cases the spleen was definitely tender, but for the most part no pain was evidenced on palpation.

In general, the recession of the size of the spleen followed the diminution in the size of the lymph nodes, but in some instances the spleen was still palpable as late as a year after the acute infection had subsided.

There was no patient in this series in whom splenomegaly was present without lymphadenopathy.

Jaundice.—Jaundice, although not a frequent complication of infectious mononucleosis, occurred in 10 of the patients in this series. It was noted that in most cases the jaundice did not occur for five or six days after the onset of the illness and in some instances was as late as ten days to two weeks in becoming evident.

The jaundice was definite in character, with icterus of the skin, scleras and mucous membranes. The urine was dark and gave a positive reaction for bile. For the majority of patients in whom jaundice was present, a diagnosis of infectious mononucleosis had already been made, and in some instances the acute febrile reaction of the disease had passed.

I have no idea what the mechanism is that produces the complication of jaundice with infectious mononucleosis. I do not feel that it is due to obstruction of the common bile duct by glandular enlargement, as there was never any change in the color of the stools or any itching of the skin. The usual duration of jaundice as a complication was not more than two weeks, and it was not in any way related to the height or duration of the fever, to the lymphadenopathy or to the splenomegaly. On examination of these patients the liver was not enlarged or tender. The majority of the students who had jaundice experienced anorexia, nausea and vomiting which lasted for a day or two.

In comparing the jaundice which complicates infectious mononucleosis with catarrhal jaundice, I was unable to note any difference in the symptoms, physical signs or clinical course.

Neurologic Signs.—Although neurologic manifestations have been described as a complication of infectious mononucleosis by Epstein and Dameshek,[9] Johansen[10] and Landes and associates,[8] no objective signs of this type were evident in any patient in this series. Headache, however, was a common symptom. In some instances it was of such severity and duration that had not a definite diagnosis of infectious mononucleosis been established a lumbar puncture undoubtedly would have been done in order to rule out involvement of the central nervous system by some other process.

Rash.—Rash occurred in only 10 patients. This is in rather sharp contrast to its occurrence in a series of 91 cases reported by Templeton and Sutherland[11] in which rash appeared in 18.5 per cent of the cases. Since a rash may occur from many different causes, it is unwise to blame a disease for the appearance of a rash which is simultaneous. Many persons manifest a rash as a result of any of a number of drugs ingested during an illness. Likewise, some persons exhibit a transient rash which is caused by fever alone.

In my experience the making of a differential diagnosis in the early stages between infectious mononucleosis and German measles is difficult. If rash is present and if there is enlargement of lymph nodes, especially of the posterior cervical nodes, which often occurs in persons suffering from German measles, the two illnesses may easily be confused. Even when laboratory studies are made, it is often impossible to be certain, since the hematologic changes may not become evident for several days. German measles, like infectious mononucleosis, is common among persons of college age, and many students in this series who were given an initial diagnosis of German measles were later found to have infectious mononucleosis.

The rash which appeared in the 10 subjects in this study closely resembled that of mild German measles, was morbilliform and transient and did not last over forty-eight hours.

Although I feel that it is wise to keep the rash in mind in connection with infectious mononucleosis, I do not feel that it is characteristic enough in itself to be relied on as a diagnostic feature.

BLOOD

The diagnosis of infectious mononucleosis cannot be made unless either the heterophile reac-

9. Epstein, S. H., and Dameshek, W.: Involvement of the Central Nervous System in a Case of Glandular Fever, New England J. Med. **205**:1238, 1931.

10. Johansen, A. H.: Serous Meningitis and Infectious Mononucleosis, Acta med. Scandinav. **76**:269, 1931.

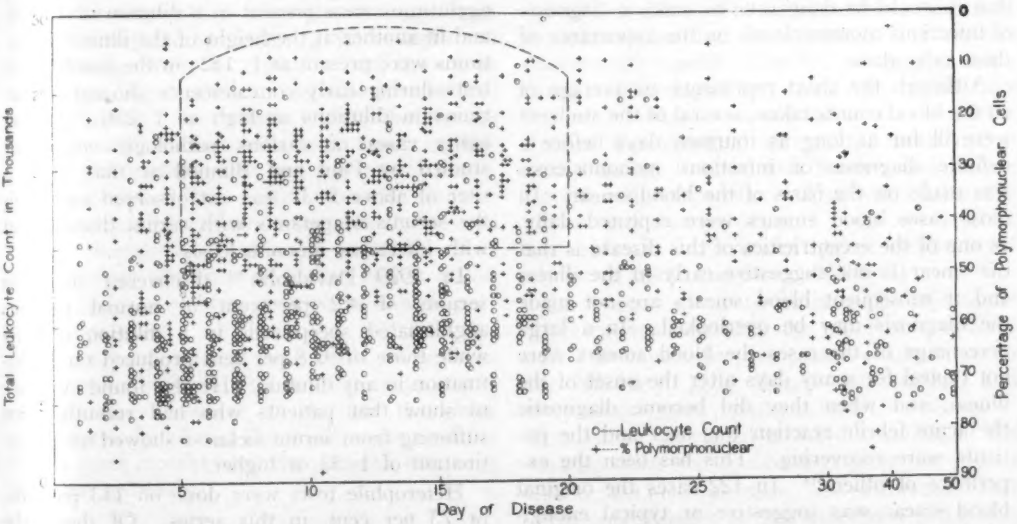
11. Templeton, H. F., and Sutherland, R. T.: The Exanthem of Acute Mononucleosis, J. A. M. A. **113**: 1215 (Sept. 23) 1939.

tion is positive in high dilution or the blood smear is typical.

In this series, the diagnosis was not made without what I consider a typical blood smear for this disease, which means that the percentage of neutrophilic cells was below 40 and in the smear there were a large number of so-called atypical lymphocytes. The atypical lymphocyte, as it appeared in these smears, was a large mononuclear cell with a pale-staining, rather fragile-looking cytoplasm that curled over on itself and had a large nucleus. It is believed by most observers that this cell is a lymphocyte. Dameshek [12] remarked that in a smear of a patient with infectious mononucleosis the size and appearance of a lymphocyte is variable.

In my experience the appearance of the smear has been easy to differentiate from that of an acute or chronic leukemia. The normal platelet count, the normal appearance of the red cells, the total absence or only occasional appearance of a cell that may be mistaken for a blast and the appearance of large numbers of atypical lymphocytes, together with a normal red cell count and normal hemoglobin content, make the diagnosis of infectious mononucleosis evident.

In 83, or 42 per cent, of the patients in this series, the initial white blood cell count was elevated above 10,000, and in 33, or 17 per cent, of these it was above 15,000. It is evident from these figures that the leukocyte count in itself is of little assistance in making an accurate diagnosis.



Blood counts of all patients with infectious mononucleosis admitted to Stillman Infirmary during the period 1935 to 1943.

If one observes the development of changes in the blood picture, it will be noted that early in the disease there is no reduction in the polymorphonuclear cell count and the so-called atypical lymphocyte appears. There may be few of these in the beginning, but they gradually become more numerous and at the same time the number of polymorphonuclear cells decreases. The reduction in polymorphonuclears may be alarming. In 1 of the patients in this study they made up only 3 per cent of the total number of white blood cells. In several cases the count was below 10 per cent, and a drop to 20 per cent was not at all unusual.

For the most part, the initial white cell count is normal or only slightly elevated. In a fair percentage of cases it may never exceed a total of 10,000. In some instances, however, it may rise far above this figure, as shown by 1 of these patients with a count of 31,000.[13] Counts above 25,000 were obtained in 7 instances. There does not seem to be any direct relationship between the total leukocyte count and the reduction of polymorphonuclear cells. In general, however, it was noted that some of the patients with higher counts had a low percentage of polymorphonuclears in the smear. Bernstein,[4] in reviewing the literature, reported 10 cases with

12. Dameshek, W.: Hematology, New England J. Med. **224**:729, 1941.

13. Since this study was completed, I have observed a patient with infectious mononucleosis with a white blood cell count of 41,000.

counts over 40,000, these occurring in children under 10 years of age.

If one observes the chart of all the blood counts taken in this series, it will be noted that on an average the leukocyte count is highest from the fifth to the twentieth day of the illness and that the reduction in the percentage of the polymorphonuclear cells also occurs during this period. The chart also shows that the abnormality in the total leukocyte count and the reduction of the polymorphonuclear cells are of short duration and return in most cases to a comparatively normal figure within two weeks. This continues gradually, so that within a period of two months the counts are back to normal. Occasionally one finds that after two months some of the atypical lymphocytes are still present in the smear, but the percentage of these is so small that it would be dangerous to make a diagnosis of infectious mononucleosis on the appearance of these cells alone.

Although the chart represents an average of all the blood counts taken, several of the students were ill for as long as fourteen days before a definite diagnosis of infectious mononucleosis was made on the basis of the blood smear. In most cases blood smears were repeated daily, as one of the eccentricities of this disease is that the smear is not suggestive early in the illness and if subsequent blood smears are not made the diagnosis may be overlooked. In a large percentage of the cases the blood smears were not typical for many days after the onset of the illness, and when they did become diagnostic the acute febrile reaction was over and the patients were recovering. This has been the experience of others.[14] In 122 cases the original blood smear was suggestive or typical enough of the disease to make an immediate, accurate diagnosis, but it must be remembered that a large number of these students did not report to the infirmary for many days after the onset of symptoms.

A few of the patients, especially those who were discharged from bed before complete recovery and whose symptoms continued for some weeks so that they were forced to return to the infirmary, were found to have a blood smear still characteristic of infectious mononucleosis. In 1 of these instance the polymorphonuclear count was reduced to a lower level than it had been at the time of the patient's original admission.

Biopsy of a cervical lymph node was performed in only 1 case. This was done, however, not because the diagnosis of infectious mononucleosis was in question but because clinical evidence showed that a tuberculous lymphadenitis might be complicating the illness. Sternal puncture was never performed as a diagnostic procedure.

14. McKinlay, C. A.: Infectious Mononucleosis, J. A. M. A. **105**:761 (Sept. 7) 1935.

HETEROPHILE TEST

Paul and Bunnell[15] in 1932 made what is considered the greatest contribution toward making an accurate diagnosis of infectious mononucleosis. Called the heterophile test, it consists of agglutinations of sheep cells with the serum of patients with the disease. At that time they demonstrated high agglutinations of sheep cells with the serums of such patients and reported 4 cases: In 1 the patient's serum agglutinated sheep cells at the high dilution of 1:1,024; in another, on the thirteenth day of the illness, agglutinins were present in a dilution of 1:128, and in another at the height of the illness agglutinins were present at 1:152; in the fourth case, tests during early convalescence showed agglutinins in dilutions as high as 1:256. Among many cases of various pathologic conditions studied by Paul and Bunnell at that time, a titer of above 1:32 was not observed except in the serums of persons with serum disease and with infectious mononucleosis.

In 1929 Davidsohn[16] discovered that the serums of 4.2 per cent of normal persons agglutinated sheep cells in a dilution of 1:4 while those of 95.8 per cent produced no agglutination in any dilution. He also found evidence to show that patients who had recently been suffering from serum sickness showed an agglutination of 1:32 or higher.

Heterophile tests were done on 143 patients, or 73 per cent, in this series. Of these, the agglutination of sheep cells occurred in a dilution of 1:64 or higher in 118 cases, and the serums did not agglutinate the cells in this dilution in 25. These 25 serums might have shown agglutination if enough tests had been done. In my experience, it was a common occurrence that a heterophile test made early during the infection might not show agglutination in a high titer while the serum from the same patient taken several days or a week later would show the presence of agglutinins in a dilution of 1:64 or higher.

With this experience, it is extremely difficult to evaluate properly the percentage of persons who are undoubtedly suffering from infectious

15. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90, 1932.

16. Davidsohn, I.: Further Studies on Heterophilic Antibodies in Serum Sickness. J. Immunol. **18**:31. 1930.

mononucleosis but who never have a positive heterophile reaction during the course of their illness. I feel, however, that such cases do occur.

In my opinion the 25 patients in this series who had a negative reaction had classic clinical infectious mononucleosis, as manifested by the symptoms, physical signs and typical blood smears. For none of them was the polymorphonuclear count higher than 40 per cent. For several the polymorphonuclear cells made up less than 15 per cent of the total count, with the greatest percentage being between 20 and 35. Moreover, the smears showed a high percentage of atypical lymphocytes.

Because of some technical reason the heterophile test was not done on 53 persons in this group, but caution was used to determine accurately the diagnosis of infectious mononucleosis. In this group the symptoms, physical signs and blood smears were as typical of the disease as were those of patients who had a positive heterophile reaction. As a matter of fact, the average of polymorphonuclear cells was lower in this group than in those that had a positive heterophile reaction. The reason for this is that patients who did not have a significantly lowered polymorphonuclear count were excluded. Had a heterophile test been done, the results would undoubtedly have been positive in a high percentage of cases.

Although an attempt was made to perform follow-up heterophile tests in this study, it was not feasible. However, in the few that were done, it was found that the results were negative within three months after the patient's discharge from the infirmary.

COMPLICATIONS

One is impressed when reading the literature by the frequent mention of complications with infectious mononucleosis. It is my feeling, however, that this disease is attended with the risk of no more complications than an ordinary infection of the respiratory tract and any complication is usually that of a concomitant infection or the exacerbation of an old process. No complication was noted in any patient in this series that could be directly attributed to infectious mononucleosis as the etiologic agent.

In 1 instance a patient acquired the syndrome of nephrosis, with large amounts of albumin in the urine, a drop in the total protein content and reversal of the albumin-globulin ratio in the blood. He also accumulated large amounts of edema fluid, including ascites. However, this patient had had the same syndrome two years before after what appeared to be an ordinary infection of the upper respiratory tract. After several weeks of rest in bed a spontaneous diuresis occurred, the edema fluid disappeared, the albuminuria cleared and the blood chemistry reverted to normal. This man is now well, with all laboratory findings normal.

Although a small amount of albumin was noted in the urine of several patients at the height of the febrile illness, this cleared quickly, and in no instance was the urine pathologic or even suggestive of an acute nephritic process.

Another patient who previously had bouts of severe diarrhea, with a positive test for occult blood in the stool, had an exacerbation of this process during an acute phase of infectious mononucleosis. Although the symptoms and the appearance of the rectal and sigmoid mucous membrane suggested early ulcerative colitis, these symptoms also cleared within a short time, only to recur some time later without any definite discoverable reason. I do not feel that the infectious mononucleosis was more responsible than any acute infection would be in the exacerbation of the intestinal symptoms; moreover, it is my feeling that nervous tension and fatigue were largely responsible. Two years later this patient still has paroxysmal bouts of diarrhea, but as far as I know the typical syndrome of ulcerative colitis has never developed.

In 1 case an acute otitis media developed about twenty days after the onset of symptoms and five days after the patient's admission to the infirmary. The abscess was incised, and streptococci were cultured from the secretion. The patient continued to have infection in the mastoid cells, and twelve days after the abscess was incised mastoidectomy was performed. This is the only instance in this series in which a bacterial infection of an ear occurred which required paracentesis and later mastoidectomy. It seems unlikely that one would attribute infectious mononucleosis as the direct cause of this complication.

Although nausea and vomiting were present in some of these patients, especially those who later acquired jaundice, it was not a prominent symptom.

Abdominal pain occurred but rarely and, with 1 exception, caused no concern as to whether an acute condition requiring surgical intervention was present. The exception was a student who twelve days after the onset of his illness and while on the way to recovery showed typical signs and symptoms of acute appendicitis. Appendectomy was performed, and an acutely inflamed appendix was removed. This was more likely a coincidental occurrence than cause and effect.

I do not feel that cardiac changes observed in patients with infectious mononucleosis can be attributed to this illness. Certainly a systolic murmur is not always indicative of pathologic conditions in the heart. It seems reasonable to assume that a systolic murmur [17] may be a coincidental finding, and, moreover, it is common knowledge that although no murmur is present when the heart rate is slow a definite systolic murmur may appear when it becomes rapid. It makes no difference whether the elevation of the heart rate is due to fever or to exercise. Bradshaw [18] reported a case of mitral stenosis following infectious mononucleosis. However, none of the patients in my group displayed any cardiac abnormality.

Gooding [19] reported 1 case of death of a patient with infectious mononucleosis as a result of bronchial pneumonia, and Du Bois [20] called attention to empyema as a complication. However, although a few of the subjects had severe cough as a predominating symptom, there was no instance of definite pneumonia.

HOSPITALIZATION

It must be remembered that the recorded days of hospitalization do not necessarily signify the duration of this illness. Many of these busy —or careless—students did not report for medical care for several days or even weeks following the onset of symptoms and reported only when their illness had reached a stage where they were unable to continue their normal activities. Even so, because of the large group in this series, it is possible to report a great diversity in the length of the hospital stay of these patients, owing of course to the extreme variability in the symptoms and clinical manifestations of the illness. Twenty-nine, or 15 per cent, of this group were hospitalized for less than five days. The greatest number, 88, or 45 per cent, were in the hospital for between six and ten days. Forty-two, or 21 per cent, were confined for a period of from ten to fifteen days; 23, or 11 per cent, from fifteen to twenty days, and 12, or 6 per cent, from twenty to twenty-five days. Two patients were obliged to remain for thirty-one days.

Discharge from the infirmary did not always indicate that the patients were ready for full activity. Many complained of extreme fatigue and easy exhaustion for several weeks after their discharge, and some were required to have a period of convalescence at home.

RECURRENCES AND RELAPSES

In any illness it is most difficult to separate a recurrence from a relapse or from a continuation of the same condition. However, in dealing with a disease as benign for the most part as infectious mononucleosis, there were many instances of a discharged patient's returning with symptoms of the same illness. Since the patients were students, the necessity for taking current examinations, intervening vacations and many other personal reasons were excuses for an early discharge, against advice.

In my experience, although a patient has a significant increase in the total white blood cell count with a definitely lowered polymorphonuclear count he may feel well and be eager to return to his normal activities. Should he be allowed to do so, it is more than possible that he would become fatigued, with a return of subjective symptoms and fever. If such is the case, it must be considered that this is a continuation of the illness, not a recurrence or a relapse. There was no instance in this series of a continuation, recurrence or relapse when I was absolutely certain that the patient had fully recovered as manifested subjectively and objectively, with at least the beginning of a return to normal of the white blood cell count and the smear. On the other hand, patients who were discharged when it was felt that more rest in bed was needed and the hemogram was still abnormal returned in a few days, or even weeks, showing again the typical syndrome of infectious mononucleosis. There were 8 such instances in this series. Four persons were readmitted to the infirmary within a period of three weeks after discharge; 2 were readmitted after a period of five weeks; 1 was readmitted after two months, and another, three months after the infection. In all of these instances the patients stated that at no time since the original discharge from the infirmary had they felt completely well and during the entire interval had had a continuation to some degree of the symptoms for which they were originally confined.

THERAPY

There is no specific therapy for infectious mononucleosis. Many of the more severe manifestations of the illness could be avoided if the patient were put to bed at once, and from experience it is my opinion that, although the symptoms

17. Contratto, A. W.: Significance of Systolic Cardiac Murmurs in College Students, New England J. Med. **228**:499, 1943.

18. Bradshaw, R. W.: Mitral Stenosis Following Infectious Mononucleosis, Ohio State M. J. **27**:717, 1931.

19. Gooding, S. E. F.: On Glandular Fever or Infectious Mononucleosis, Practitioner **127**:468, 1931.

20. Du Bois, A. H.: Pathogenesis of Monocytic Angina, Acta med. Scandinav. **73**:237, 1930.

may be mild, rest in bed and the usual symptomatic treatment are the wise approach.

In cases of severe headache or extreme discomfort of the throat, codeine in doses of ½ or 1 grain (0.03 or 0.06 Gm.) by mouth every four hours was needed. Irrigations with saline solution were administered for sore throat. For ulcerations of the throat or Vincent's angina hydrogen peroxide diluted 1 to 3 was found helpful if used as a wash every two hours. Although neoarsphenamine has been used in therapy for this illness by oral application and intravenously, I do not believe it is necessary or helpful. Likewise, in the few cases in this series in which sulfadiazine was administered, no benefit was noted. Nicotinamide seemed to relieve some patients who had severe Vincent's angina. Excess salt was given to patients who had profuse sweating. In persons in whom jaundice occurred accompanied by nausea and vomiting it was necessary to replenish body fluids, salt and dextrose by intravenous injection. Also, in some instances in which the condition of the patient's throat was such that swallowing was painful, intravenous injections of dextrose and isotonic solution of sodium chloride were used with great benefit.

It is desirable to emphasize the convalescent period to patients discharged from a hospital after this illness. The simple therapy of enough rest, sleep, proper diet and fresh air will certainly hasten the return to normal from a disease in which extended fatigue is the most insidious effect. This is especially true of young people, who have the greatest affinity for infectious mononucleosis, since they are at the present time leading particularly strenuous lives.

CONCLUSIONS

Infectious mononucleosis is a benign illness.

The complications encountered in this series were varied, but they are believed not to be directly referable to the disease.

Infectious mononucleosis may be accompanied notably by lymphadenopathy, splenomegaly, jaundice, Vincent's angina, ulcerations of the throat, fever, a conspicuous change in the blood picture and a number of complaints identical with those common to an ordinary infection of the upper respiratory tract.

Accurate diagnosis is difficult because of the variability of the symptoms and clinical manifestations. The problem and major difficulty in this disease is the making of a differential diagnosis, which can easily be accomplished by the heterophile test, blood count and smear. I have pointed out the importance of making not only more than one but frequent tests and smears during the course of the illness, since a peculiarity of infectious mononucleosis is that there is more often than not a delay of days or even weeks before the hematologic changes are conclusive enough to permit an accurate diagnosis.

SPONTANEOUS PNEUMOTHORAX COMPLICATING BRONCHIAL ASTHMA

REPORT OF TWO CASES AND CONSIDERATION OF POSSIBLE MECHANISMS INVOLVED IN ITS PRODUCTION

MASON TROWBRIDGE JR., M.D.*
ELLSWORTH, MAINE

Spontaneous pneumothorax is a potentially fatal complication of bronchial asthma, the diagnosis of which may not be obvious. In a recent review of the world literature on this subject Maccone [1] collected 27 cases. Piaggio Blanco and García Capurro [2] suggested that the ease with which this condition may be missed accounts for its apparent rarity. Although most authors have failed to mention bronchial asthma as a precursor of spontaneous pneumothorax, the casual manner in which others [3] have mentioned it does not indicate extreme rarity. Questioning of physicians has revealed several who have observed one or more unreported cases.

Spontaneous pneumothorax occurs as a complication of bronchial asthma chiefly in young persons, of both sexes. The average age of the patients whose cases were collected by Castex and Mazzei [4] was 32 years, and they did not include the children of 1¼ and 2 [5] and 4 [6] years of age whose cases were reported elsewhere. The oldest reported patient was 59 years of age.[7] The mode of onset is as variable as that of spontaneous pneumothorax occurring in otherwise normal persons.[8] Bottero [9] suggested that the symptoms may depend on the rapidity of the development of the pneumothorax. Dyspnea is usually present and definitely subjectively different from that ordinarily accompanying asthmatic attacks.[10] Pain is an almost constant feature, but it may be absent, particularly in cases of recurrent pneumothorax. It is usually pleural and may radiate to the flank; a sense of constriction in the chest is frequently noted. Casiello [10] reported a case in which the clinical picture suggested a coronary occlusion. Though there may be no symptoms to suggest the development of a pneumothorax during an asthmatic attack,[11] the time of onset of the pneumothorax can usually be established by the onset of pain or of a changing type of dyspnea. Left-sided pneumothorax is slightly more common than right. The condition often recurs on the same [12] or on the opposite [13] side. Four cases of bilateral

* Formerly intern, First Medical Division, Bellevue Hospital, New York, I. Ogden Woodruff, M.D., Director.

1. Maccone, V.: Il pneumotorace spontaneo nell'asma, Ann. Ist. Carlo Forlanini **4**:257 (March-April) 1940.

2. Piaggio Blanco, R. A., and García Capurro, F.: Neumotórax espontáneo y enfisema subcutáneo y del cuello en el curso del asma, Arch. urug. de med., cir. y especialid. **16**:367 (April) 1940.

3. (*a*) Myers, J. A.: Diseases of the Chest, edited by M. Fishbein, New York, National Medical Book Company, Inc., 1935. (*b*) Rowe, A. H.: Bronchial Asthma, in Nelson's Loose Leaf Medicine, New York, Thos. Nelson & Sons, 1937, vol. 3, p. 457. (*c*) Hamman, L.: A Note on the Mechanism of Spontaneous Pneumothorax, Ann. Int. Med. **13**:923 (Dec.) 1939.

4. Castex, M. R., and Mazzei, E. S.: Pneumothorax spontane dans l'asthme, Presse méd. **46**:529 (April 6) 1938.

5. Rasenack, W.: Ueber 20 Fälle von Spontanpneumothorax im Kindesalter, Ztschr. f. Kinderh. **58**:95, 1936.

6. Gunther, cited by Bottero.[9]

7. Faulkner, W. B., Jr., and Wagner, R. J.: Fatal Spontaneous Pneumothorax and Subcutaneous Emphysema in an Asthmatic, J. Allergy **8**:267 (March) 1937.

8. Leggett, E. A.; Myers, J. A., and Levine, I.: Spontaneous Pneumothorax; Report of Thirty-One Cases, Am. Rev. Tuberc. **29**:348 (March) 1934.

9. Bottero, A.: Il pneumotorace spontaneo negli asmatici, Athena **8**:372 (Aug.) 1939.

10. Casiello, A.: Neumotórax espontáneo benigno y asma, Arch. argent. de enferm. d. ap. respir. y tuberc. **5**:164 (March-April) 1937; Neumotórax espontáneo benigno y asma, Rev. méd. del Rosario **26**:961 (Oct.) 1936.

11. (*a*) Emerson, C. P., and Beeler, R. C.: An Unusual Case of Double Spontaneous Pneumothorax, Am. J. Roentgenol. **10**:126 (Feb.) 1923. (*b*) Spivacke, C. A.: Asthma with Pneumothorax, M. J. & Rec. **122**:10 (July 1) 1925.

12. (*a*) Maccone.[1] (*b*) Harvey, C.: Asthma Complicated by Spontaneous Pneumothorax, M. J. Australia **2**:950 (Dec. 3) 1938. (*c*) Argüelles Casals, C.; Alvarez García, V., and Pedraza, R. O.: Neumotorax espontaneo en el asma, Rev. de cien. méd. **1**:90 (Sept.) 1938. (*d*) Fornet, B.: Rezidivierender Spontanpneumothorax bei Bronchialasma, abstracted, Zentralbl. f. d. ges. Tuberk.-Forsch. **33**:62 (June) 1930. (*e*) Fuchs, A. M.: Spontaneous Pneumothorax in an Asthmatic Treated with Iodized Oil, New York State J. Med. **39**:791 (April 15) 1939. (*f*) Symes-Thompson, H. E.: Spontaneous Pneumothorax, Lancet **2**:791 (Oct. 11) 1930.

13. Ribeiro de Carvalho, J., and da Silva Lacaz, C.: Pneumothorax expontaneo bilateral por emphysema asthmatico, Ann. paulist. de med. e cir. **37**:241 (March) 1939.

involvement have been reported.[14] In 4 cases bronchial asthma was complicated not only by pneumothorax but by subcutaneous emphysema.[15]

In many cases the physical signs are those that might be expected. However, Elliott [15a] asserted that there were no signs suggesting a pneumothorax in his patient, and McGuire [16] reported that the physical signs of a pneumothorax appeared only after some weeks. Cyanosis is usually present, and orthopnea is not uncommon. Patients are afebrile except with an associated bronchopneumonia [17] or pleural effusion,[12e] both of which complications have been reported only once. Small amounts of nonfibrinous pleural fluid are often noted.[1] There is no consistent abnormality of the pulse, respiration or blood pressure.

Seven deaths from spontaneous pneumothorax complicating bronchial asthma have been reported.[18] However, the condition is usually benign, the lung reexpanding without aspiration of pleural air within a few weeks. One pneumothorax persisted for thirty years.[19]

The role of pulmonary and interstitial emphysema in this type of pneumothorax will be considered later in the paper. No association with pulmonary tuberculosis has been noted. Chronic sinusitis and bronchitis do not appear to be predisposing factors. In all adults with the condition the asthma had been present for several years.

The blood count and the urine are normal and serologic tests for syphilis give negative results, though leukocytosis may occur with the complications noted that cause fever.

Roentgenograms may fail to reveal the pneumothorax.[2] No roentgenographic evidence of mediastinal emphysema was noted in the previously reported cases.

14. Faulkner and Wagner.[7] Emerson and Beeler.[11a] de Carvalho and da Silva Lacaz.[13] Jeffrey and Marlatt.[33]

15. (*a*) Elliott, R. W.: Subcutaneous Emphysema and Pneumothorax in Bronchial Asthma, Lancet **1**:1104 (May 14) 1938. (*b*) Piaggio Blanco and García Capurro.[2] (*c*) Faulkner and Wagner.[7] (*d*) Casiello.[10]

16. McGuire, H. H.: A Case of Pneumothorax Occurring in Bronchial Asthma, Virginia M. Monthly **51**:167 (June) 1924.

17. Kahn, I. S.: Spontaneous Pneumothorax Due to Bronchial Asthma: Case Report, Texas State J. Med. **28**:781 (March) 1933.

18. (*a*) Rey, A. J.; Rey, J. C., and Lértora, E.: Neumotórax espontáneo y asma, Rev. argent. de tuberc. **5**:167 (July-Sept.) 1939. (*b*) Nash, W. G.: Surgical Emphysema in a Fatal Case of Influenza, Brit. M. J. **1**:9 (Jan. 4) 1919. (*c*) Fisher, R. L.: Non-Tuberculous Spontaneous Pneumothorax, Ann. Int. Med. **4**:1395 (May) 1931. (*d*) Austoni, M., and Marfori, L.: Considerazioni critiche su 33 casi di pneumatorace spontaneo, Policlinico (sez. med.) **46**:113 (March) 1939. (*e*) Faulkner and Wagner.[7] (*f*) Emerson and Beeler.[11a] (*g*) Gunther.[6]

19. Mainini, C., and Alvarez, A.: A propósito de un caso de neumotórax total espontáneo benigno de 30 años de duración. Recuperación de las funciones respiratorias por expansión parcial y eficiente del pulmón colapsado, Prensa méd. argent. **22**:1411 (July 24) 1935.

REPORT OF CASES

CASE 1.—A 39 year old Spanish American man was admitted to the first medical division of Bellevue Hospital on April 7, 1939, with a chief complaint of increasing dyspnea during an asthmatic attack.

Past History.—He had had asthma for nine years, chiefly in the spring and summer, and had attended two allergy clinics in New York. He had had many cutaneous tests, the results of which were apparently inconclusive. Emotional upsets, strong odors and infections of the respiratory tract were named as factors in bringing on asthmatic attacks. There was no history suggesting chronic sinusitis or pulmonary disease, and the system review revealed no other significant past history.

Family History.—There was no history of allergy or of any thoracic catastrophe suggesting a pneumothorax.

Present Illness.—Two weeks prior to the patient's admission an asthmatic attack developed following an infection of the upper respiratory tract. The asthma persisted throughout this period, and he obtained only transient relief from frequent subcutaneous injections of epinephrine. He had a steady severe cough. Twelve hours before admission there was a sudden onset of dyspnea of a type that was definitely different from that accompanying asthmatic attacks. He experienced no pain but came to the hospital when breathing seemed almost impossible.

Physical Examination.—The temperature was 100 F., the pulse rate 100, the respiratory rate 30 and the blood pressure 120 systolic and 75 diastolic. The patient was a thin man who continued to be dyspneic, cyanotic and orthopneic after nasal administration of oxygen. There was no evidence of infection of the nasopharynx or nasal sinuses. The trachea was in the midline, and there was no subcutaneous emphysema. The initial examination of the chest revealed only typical signs of bronchial asthma. No difference between the right and the left side of the chest was noted. Seven hours later the sibilant expiratory breath sounds had abated, and the breath sounds were greatly diminished on the right side. The entire chest was hyperresonant, but particularly so on the right side. There were a positive coin sound and lag on the right. When the patient breathed deeply, many sibilant expiratory rales were heard over both sides of the chest, and there was only slight diminution of the intensity of the breath sounds on the right side.

Laboratory Studies.—The urine gave a 2 plus reaction for albumin but otherwise was normal. The hemoglobin content of the blood was 16 Gm. per hundred cubic centimeters. The red cell count was 5,200,000 and the white cell count 12,400, with polymorphonuclear leukocytes 62 per cent, lymphocytes 30 per cent, monocytes 4 per cent and eosinophils 4 per cent. The Wassermann reaction of the blood was negative.

Roentgen Examination.—Fluoroscopy several hours after the patient's admission to the hospital revealed an almost complete collapse of the right lung without marked mediastinal shift. Roentgenograms taken two weeks later (after aspiration of air) showed a pneumothorax on the right side, with a 60 per cent collapse

of the lung, irregular adhesions at the base and a small amount of fluid in the costophrenic sinus.

Clinical Course.—The patient was treated with subcutaneous injections of epinephrine hydrochloride and nasal inhalations of oxygen. Several hours after he entered the hospital the pneumothorax became evident on physical examination. Twenty-four hours after his admission nonpleuritic costovertebral pain on the right side, vomiting and increased dyspnea made the aspiration of 300 cc. of pleural air necessary. The intrapleural pressure was plus 3, plus 11 before the aspiration and minus 2, plus 2 afterward. The pain, dyspnea and vomiting persisted with diminishing severity for two weeks, and there was no striking relief from aspiration of pleural air. Five days after the patient's admission the initial pleural pressure was minus 6, plus 11, and after aspiration of 700 cc. of air, minus 8, plus 8. At the end of two weeks there was almost complete expansion of the lung, with no further pulmonary symptoms. He was discharged on the fiftieth day of hospitalization, and although he was readmitted several times with the diagnosis of bronchial asthma and pulmonary emphysema, there was no recurrence of the pneumothorax.

Case 2.—A 33 year old American seaman was admitted to the first medical division of Bellevue Hospital Sept. 8, 1938, with a history of several days of cough and asthma.

Past History.—The patient had had a chronic cough throughout most of his adult life and had had asthmatic attacks for five to six years. On his first admission to the hospital, in 1935, the admission diagnosis was chronic bronchitis, malnutrition, fatty liver, chronic alcoholism and possible bronchial asthma. In 1936 he was admitted with the diagnosis of acute and chronic bronchitis and bronchial asthma. The asthma responded to oral administration of ephedrine sulfate. In 1938 a hemorrhoidectomy was postponed because of an exacerbation of bronchitis. There was no history of pulmonary tuberculosis, and a roentgenogram of the chest taken in 1935 revealed no sign of this disease. The patient said he had been a heavy drinker but that he had not indulged in alcoholic excesses in recent years. Except for gonorrhea at the age of 17, the system review revealed no significant past history.

Present Illness.—Six days prior to admission the patient became increasingly short of breath during an asthmatic attack. He was gasping for air, and a physician gave him a hypodermic injection which temporarily relieved the dyspnea. Throughout the week, however, he became increasingly dyspneic, had constant anorexia and vomited on one occasion. There was no mention of pain prior to his admission.

Physical Examination.—The temperature was 100.2 F., the pulse rate 120, the respiratory rate 30 and the blood pressure 120 systolic and 80 diastolic. The patient was a poorly nourished man appearing acutely and chronically ill, dyspneic, cyanotic and orthopneic. A postnasal discharge was noted. The chest was emphysematous, and prolonged high-pitched expiratory breath sounds and sibilant wheezes were heard bilaterally. The heart was normal except for the absence of an apical impulse in the usual location and the presence of an epigastric pulsation. Cardiac auscultation was unsatisfactory because of the loud breath sounds.

Laboratory.—Urinalysis gave normal results. The white blood cell count was 8,850, with polymorphonuclear leukocytes 70 per cent, lymphocytes 28 per cent, monocytes 1 per cent and eosinophils 1 per cent.

Clinical Course.—During the first twenty-four hours the clinical picture was that of bronchial asthma which failed to respond to the routine therapy for this condition. One observer confirmed the presence of signs of bronchial asthma bilaterally, and another noted that the wheezing was more pronounced on the left side of the chest. There was no tracheal deviation and no engorgement of the veins of the neck or dependent edema. The cyanosis noted on the patient's admission increased. Thirty-six hours after his admission the vital capacity was 1,500 cc. At about this time the chest began to "ache." The bronchospasm had not been relieved by epinephrine, ephedrine or ammonium chloride, and he was given a total of 0.6 Gm. of sodium amytal over an eleven hour period. Because of extreme restlessness, a total of 20 cc. of paraldehyde was given orally over a seven hour period. After this medication he insisted on walking about the ward but was apparently well oriented. Three hours later deep cyanosis was noted; the pulse rate was 84 per minute, and respiration was shallow, with a rate of 24 to 30 per minute. The pulse became feeble, and epinephrine and pentamethylenetetrazol (metrazol) and also intravenous injections of 50 per cent dextrose solution were administered without effect. It was noted that the physical signs suggesting bronchospasm were abating and that the right hemithorax was poorly aerated. He was placed in a Drinker respirator. The cyanosis deepened, and he became comatose and failed to respond to noxious stimuli after two hours. After four hours in the respirator, sixty hours after admission, he died. Just prior to his death large amounts of grayish mucus were aspirated from the trachea. "This probably explains the markedly diminished aeration of the right lung" was one of the last notes made on the chart.

The temperature ranged from 97 to 100.2 F., the pulse rate from 90 to 100 and the respiratory rate from 24 to 30, except for terminal figures of 101 F., 120 and 60 respectively.

Permission for necropsy was not obtained.

Twenty-four hours after the death of the patient the routine roentgenogram of the chest taken on his admission was reported as showing "pneumothorax resulting in partial collapse of the right lung; minimal effusion in the costophrenic sinus; interstitial changes and fibrosis at the roots of both lungs, extending into the parenchyma; fusiform dilatation of the descending portion of the arch of the aorta."

COMMENT

In case 1 the diagnosis of spontaneous pneumothorax was not made during the asthmatic attack because insufficient importance was attached to the patient's statement that there was a sudden change in the character of his dyspnea. Also, as Laennec[20] has pointed out, the diagnosis of pneumothorax in an emphysematous person may be difficult because of the diffuse hyperresonance and distant breath sounds. As has been observed elsewhere,[10] sibilant asthmatic breath sounds were heard with great clarity over the pneumothorax.

In case 2 several observers noted physical signs that should have suggested the correct

20. Laennec, R. H. T.: De l'auscultation mediate, Paris, J. A. Brosson & J. S. Chaude, 1819.

diagnosis. But the minds of those who saw the patient seemed closed to the possibility of a pneumothorax occurring during an asthmatic attack. It is possible, but unlikely, that death resulted from unwise administration of paraldehyde.[21] Had the diagnosis of pneumothorax been made, it is likely that appropriate therapy might have saved the patient. The use of the respirator was, of course, ill advised.

On few occasions is the physician's "index of suspicion" lower than when he is treating recurrent bronchial asthma. Roentgenograms cannot be ordered with every attack, and it was only by chance that in the second case a routine film taken on the patient's admission revealed the pneumothorax after his death. The large number of interesting medical and surgical methods of treating bronchial asthma tend to direct one's attention toward therapy rather than toward a consideration of a possible concomitant pathologic process. The clinical picture of an asthmatic patient with pneumothorax may be so alarming that the problem of relief of bronchospasm occupies the entire attention of the physician.

In both the cases reported here there was an associated chronic bronchitis and pulmonary emphysema. There is no evidence to suggest that the mechanism of the pneumothorax in the second case was any other than the usually accepted one of a rupture of the visceral pleura with a subsequent valvular action. In the first case the second manometric readings suggest an open pneumothorax, as in the case of Kahn.[17] At no time was the relief of symptoms from the aspiration of pleural air striking. The significance of this unusual feature of the pneumothorax in the first case will be discussed after a consideration of the newer knowledge of certain mediastinal air pathways.

Laennec[20] described interstitial emphysema, but until recent years the subject has received little attention. Discussing spontaneous pneumothorax in asthma, Hamman[3c] stated: ". . . one is justified in considering that the pneumothorax may be secondary to mediastinal emphysema." Elsewhere,[22] discussing spontaneous pneumothorax, he stated: "It seems altogether likely that in most instances, if not in all, the air reaches the pleural cavity through the mediastinum. . . . We have been accustomed to ascribe the escape of air to the rupture of emphysematous bullae and to minute tears produced by the tug of adhesions. These explanations have never been altogether convincing, and I think that we must now at least entertain the possibility that the initial lesion of a spontaneous pneumothorax may be interstitial emphysema of the lung with an escape of air to the pleura through the mediastinum." Several features of the reported cases of spontaneous pneumothorax and asthma support Hamman's contention. It has been noted that subcutaneous emphysema of the neck may be associated with spontaneous pneumothorax and asthma, a fact which suggests the possibility of mediastinal pathways for air. (Seventeen collected cases of subcutaneous emphysema and bronchial asthma[23] make this condition appear somewhat more unusual than spontaneous pneumothorax as a complication of asthma. Experimentally, however, interstitial air tends to travel from the periphery to the mediastinum rather than to the pleural space.[22])

Aspiration of the pleural air in this type of pneumothorax may not relieve the symptoms.[23a] This suggests that there may be some cause for cardiorespiratory embarrassment other than the compression of the lung. I recall seeing a patient with bilateral spontaneous pneumothorax with obliteration of the right radial pulse following tracheotomy. The extreme cyanosis and dyspnea were not relieved by aspiration of pleural air. Obliteration of the radial pulse has been reported to occur with spontaneous pneumothorax complicating bronchial asthma.[7] It is possible in these cases of bronchial asthma, as in the case of pneumothorax following tracheotomy, that aspiration of pleural air failed to relieve an associated mediastinal emphysema.

Pastorino,[24] writing on spontaneous pneumothorax and asthma in 1934, suspected the existence of bronchovascular pathways for air through the mediastinum. Their exact location was later demonstrated by Macklin. He introduced air under pressure into the terminal bronchi of cats and followed its course histologically. This experiment reproduced roughly the conditions in asthma when air is trapped under pressure in the smaller ramifications of the bronchial tree. He stated,[25] referring to air under pressure in the alveoli: ". . . there is a break through from the overdistended alveoli of the

21. Burstein, C. L.: The Hazard of Paraldehyde Administration: Clinical and Laboratory Studies, J. A. M. A. **121**:187 (Jan. 16) 1943.

22. Hamman, L.: Spontaneous Mediastinal Emphysema, Bull. Johns Hopkins Hosp. **64**:1 (Jan.) 1939.

23. Rosenberg, J., and Rosenberg, L.: Subcutaneous Emphysema Complicating Bronchial Asthma, Am. J. M. Sc. **195**:682 (May) 1938.

23a. Harvey,[12b] Elliott,[18a] Case 1 of present report.

24. Pastorino, A.: Asma y enfisema; asma y neumotórax, Rev. de tuberc. d. Uruguay **4**:256, 1934.

25. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum: Clinical Implications, Arch. Int. Med. **64**:913 (Nov.) 1939.

lung into the overlying perivascular sheaths . . . multiple very small ruptures into the sheath system which overlie the finer ramifications of the pulmonary blood vessels." Once entrance has been gained to the perivascular sheaths, air can travel to the pleural space, to the mediastinum and neck, and even to the retroperitoneal space. Bronchoscopic studies during asthmatic attacks [25a] indicate that there is sufficient obstruction from bronchial constriction, edema and fibrin plugs to build up alveolar pressure. Macklin [26] stated that the pressures produced in his experiments were greater than might be encountered clinically. But the passage of air to the pleural space in accidental overinflation of the lung during intratracheal anesthesia [27] suggests the possibility of alveolar rupture and escape of air into the perivascular sheaths occurring in human beings as in experimental animals. The similarity of bronchial asthma complicated by pneumothorax and subcutaneous emphysema and the conditions observed in the experimental animals of Macklin also suggests that interstitial emphysema may occur as a complication of bronchial asthma. The similarity between cases of asthma thus complicated and cases in which there are pneumothorax and mediastinal emphysema secondary to a foreign body in a bronchus [28] is striking. In the latter cases it can be shown that the air enters the pleural space not through the visceral pleura but via the damaged alveoli.

However, the possibility that this type of pneumothorax may be secondary to rupture of a subpleural bleb cannot be dismissed, particularly since long-standing bronchial asthma and "asthmatic bronchitis" may be associated with pulmonary emphysema. But most authors state that spontaneous pneumothorax as a complication of bronchial asthma is rare in the presence of pulmonary emphysema.[29] The usual hypothesis advanced is that emphysematous tissue is more rigid than normal pulmonary tissue and resists compression. Cournand, Richards and Maier [30] have reported on a patient in whom healthy tissue was compressed by a pneumothorax (artificial) whereas the emphysematous tissue was not. This fact makes spontaneous pneumothorax a particularly grave complication of pulmonary emphysema. Three autopsies on patients dying from spontaneous pneumothorax and bronchial asthma have been reported. Emerson and Beeler [11a] reported the presence of an associated pulmonary emphysema. Fornet [12d] described subpleural interstitial emphysema with lacerated alveoli. Austoni and Marfori [18d] mentioned both pulmonary and interstitial emphysema with no demonstrable pleural lesion. A necropsy was not performed in Nash's fatal case,[18b] but he described a mediastinal resonance suggesting " . . . an escape of air from the lower trachea or bronchus into the mediastinum." Reports of 14 autopsies on persons dying during asthmatic attacks [31] mentioned "voluminous lungs" frequently but not interstitial emphysema. Macklin [25] stated that interstitial emphysema is rarely recognized without special intrabronchial fixation of the tissues. An unsuspected pneumothorax may easily be missed at autopsy. Rasmussen and Adams [32] expressed the belief that mediastinal and interstitial emphysema may be the cause of death in certain cases of bronchial asthma and have experimental evidence to support their contention. Macklin [26] stated that experimental interstitial emphysema may involve the opposite lung and that once a pneumothorax is established a contralateral pneumothorax may occur after a break through the thin mediastinal septum. This fact makes it unlikely that the relatively high incidence of bilateral pneumothorax in asthma previously referred to, is caused by bilateral "simultaneous rupture of bullae on the surface of the lungs," as has been suggested.[33] Fuchs [12e] reported a case of spontaneous pneumothorax occurring in an asthmatic patient after the intrabronchial instillation of iodized oil. Roentgenograms showed no oil in the pleural space, and the author suggested that the air

25a. Leggett.[8] d'Abreu, A. L.: Asthmatic Attack Studied Through Bronchoscope, Lancet **2**:421 (Oct. 5) 1940.

26. Macklin, C. C.: Pneumothorax with Massive Collapse from Experimental Over-Inflation of the Lung Substance, Canad. M. A. J. **36**:414 (April) 1937.

27. Heidrick, A. F.; Adams, W. E., and Livingstone, H. M.: Spontaneous Pneumothorax Following Positive Pressure Intratracheal Anesthesia: Report of a Case, Arch. Surg. **41**:61 (July) 1940.

28. Fisher, J. H., and Macklin, C. C.: Pulmonic Interstitial and Mediastinal Emphysema: Report of a Fatal Case in Which the Emphysema Occurred in a Child as a Result of the Aspiration of Peanut Fragments, Am. J. Dis. Child. **60**:102 (July) 1940.

29. Castex and Mazzei.[4] Faulkner and Wagner.[7] Casiello.[10] Rey, Rey and Lértora.[18a] Pastorino.[24]

30. Cournand, A.; Richards, D. W., and Maier, H. C.: Pulmonary Insufficiency, Am. Rev. Tuberc. **44**:272 (Sept.) 1941.

31. Craige, B.: Fatal Bronchial Asthma: Report of Seven Cases, Arch. Int. Med. **67**:399 (Feb.) 1941. Bases, L., and Kurtin, A.: Prevention of Death in Status Asthmaticus: Value of Bronchoscopy, Arch. Otolaryng. **36**:79 (July) 1942.

32. Rasmussen, R. A., and Adams, W. E.: Experimental Production of Emphysema, Arch. Int. Med. **70**: 379 (Sept.) 1942.

33. Jeffrey, G. S., and Marlatt, D. C.: Simultaneous Bilateral Spontaneous Pneumothorax Complicating Bronchial Asthma, Canad. M. A. J. **39**:171 (Aug.) 1938.

escaped from distended bronchioles rather than through the surface of the visceral pleura.

A concomitant mediastinal and interstitial emphysema may explain the extreme degree of cardiorespiratory embarrassment in cases of spontaneous pneumothorax and bronchial asthma when the symptoms persist after aspiration of pleural air and relief of bronchospasm. Macklin[25] stated that air in the perivascular sheaths acts as "an air vise" and may interfere with both the arterial and the venous blood supply with resulting failure of the right side of the heart. Ballon and Francis,[34] in conclusions drawn from both clinical and experimental material, stated that mediastinal air not only may cause cardiac tamponade but may compress even the axillary and femoral vessels. They reported edema of the trachea and bronchi in mediastinal emphysema, a fact which would make mediastinal emphysema a particularly disastrous complication of bronchial asthma.

Most authors favor conservative management of bronchial asthma complicated by spontaneous pneumothorax. Aspiration of pleural air is usually not necessary. If there is evidence of mediastinal or interstitial emphysema, it may be advisable to maintain the pneumothorax to stop the leak of air rather than to aspirate pleural air.[35] Although the administration of morphine to patients with bronchial asthma is usually not condoned, it may be necessary to use this drug to stop a cough that is building up intra-alveolar pressure. No definite outline of therapy can be given, since individual cases vary greatly in respect to associated pulmonary and interstitial emphysema, bronchial infection and numerous other factors. Although mediastinal emphysema is usually a benign condition, it should be noted that surgical release of mediastinal air may be necessary.[25] Surgical treatment was not suggested by any of the authors writing on spontaneous pneumothorax complicating bronchial asthma, but it might be indicated for a moribund patient. The use of dextrose solution intrapleurally has been suggested to prevent the frequent recurrence of spontaneous pneumothorax in asthmatic persons.[12b]

34. Ballon, H. C., and Francis, B. E.: Consequences of Variations in Mediastinal Pressure: Mediastinal and Subcutaneous Emphysema, Arch. Surg. **19**:1627 (Dec.) 1929.

35. Harvey.[12b] Macklin.[25]

SUMMARY

Spontaneous pneumothorax occurred as a complication of bronchial asthma in 2 cases. This is a potentially fatal complication of bronchial asthma. Its diagnosis is extremely difficult in certain cases. This complication should be considered in every case of intractable or atypical asthma. Spontaneous pneumothorax and bronchial asthma are probably sometimes associated with mediastinal and interstitial emphysema.

NUTRITIONAL PROBLEMS PRESENTED BY A PATIENT WITH EXTENSIVE JEJUNOILEITIS

SAMUEL T. KILLIAN, M.D., AND FRANZ J. INGELFINGER, M.D.
BOSTON

Granulomatous jejunoileitis and its clinical manifestations have been well described,[1] but less attention has been devoted to some of the nutritional problems which may attend this disease. The nature of these problems is well exemplified by the case of a patient recently under our observation. Not only were the functions of his small intestine impaired by an extensive granulomatous process, but he suffered from severe hypoproteinemia, partly induced by a period of semistarvation in an open lifeboat. This report presents the results of various therapeutic measures which were evaluated on the basis of the patient's clinical course, daily nitrogen balances and other laboratory data obtained over a period of forty-two weeks.

REPORT OF A CASE

R. D., a 23 year old white American man, was admitted to the Evans Memorial Hospital on July 28, 1942, with the chief complaint of diarrhea of three months' duration. His past history was noncontributory. At no time did he have any gastrointestinal disturbance. His weight, however, which six years previously had been 180 pounds (81.6 Kg.), dropped to 140 pounds (63.5 Kg.) in the three to four years immediately preceding entry to the hospital.

Thirteen weeks before the patient was admitted to the hospital, the ship on which he was serving as a mess boy was torpedoed. Subsequently he was exposed in an open lifeboat for eight days and had to subsist on small rations of chocolate, malted milk tablets, biscuits and water. During the last two days of this ordeal, his ankles began to swell, although in none of the other men in the lifeboat did this condition develop. After the group was rescued, the patient had his first bowel movement in eight days. He was thereafter received at a small hospital on the eastern coast of the United States, where he remained for two months. For the first five weeks of his course there he had four to five small, watery bowel movements daily. These contained a small amount of blood on rare occasions. Thereafter the movements decreased to two a day. He was treated with a limited dietary intake and orally administered vitamins and received one blood transfusion. During these two months he lost approximately 14 pounds (6.4 Kg.) in weight.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

1. (*a*) Crohn, B. B., and Yunich, A. M.: Ileojejunitis, Ann. Surg. **113**:371-380 (March) 1941. (*b*) Sussman, M. L., and Wachtel, E.: Granulomatous Jejuno-Ileitis, Radiology **39**:48-53 (July) 1942.

The patient was transferred to a Marine hospital on June 17, 1942, where he was found to be emaciated and dehydrated. Pitting edema of the ankles extended one third of the way to the knees. The tongue was smooth but not sore. During the first seventeen days, a septic type of fever (the temperature rising to 102 F.) was present, but thereafter the course was afebrile. Laboratory data on his admission to the hospital were as follows: red blood cell count, 1,200,000; hemoglobin content, 54 per cent; hematocrit value, 22 per cent, and reticulocyte count, 1.4 per cent. A halometer reading showed the red blood cells to average 8.4 microns in diameter. The white blood cell count was 3,200 with a differential count of 33 per cent polymorphonuclear leukocytes, 65 per cent lymphocytes and 2 per cent eosinophils. The icterus index was 2 and the sedimentation rate was 6 mm. in one hour (normal). The serum total protein content was 4.85 Gm. per hundred cubic centimeters, with 2.34 Gm. of albumin and 2.51 Gm. of globulin. The urine was normal except for a trace of albumin. Gastric analysis showed absence of free hydrochloric acid after stimulation with histamine. There were no ova or parasites in the stools; fat was present, but the exact amount was not determined.

The patient was considered to have sprue or pernicious anemia and was therefore given daily parenteral injections of liver extract and vitamin B complex. Diarrhea stopped on the second day of this therapy. The red blood cell count began to rise, and the reticulocyte count reached 12 per cent after ten days. After the red blood cell count reached 3,000,000, the patient began to have diarrhea again, with loss of weight. After three blood transfusions, some improvement occurred and the red blood cell count rose to 4,300,000 with a hemoglobin content of 78 per cent. The reticulocyte count gradually decreased to 1.3 per cent. The total white blood cell count and the differential count returned to normal values within two weeks. The serum total protein content decreased slightly to 4.7 Gm. per hundred cubic centimeters, with albumin 2.15 Gm. and globulin 2.55 Gm. An oral dextrose tolerance test showed the fasting blood sugar level to be 49 mg. per hundred cubic centimeters; one-half hour after ingestion of 100 Gm. of dextrose the level was 106 mg.; at three hours, 67 mg., and at four hours, 50 mg. Roentgenograms of the skull, sternum, pelvis and chest revealed no abnormalities. Gastrointestinal roentgen studies showed the stomach to be normal. In six hours the barium sulfate had reached the sigmoid region, but a considerable amount of it was retained in the ileum, the mucosal pattern of which was suggestive of ulcerative enteritis. A roentgenogram after a barium enema revealed normal conditions.

On July 28 the patient was transferred to the Evans Memorial Hospital for further study. He was a tall, well developed but moderately emaciated young man who weighed only 113 pounds (51.3 Kg.). The eyes, ears, nose and throat were not unusual. The tongue was normal. The lungs and heart were within normal

limits. The blood pressure was 124 systolic and 76 diastolic. There was moderate abdominal distention with tympany; tenderness was not present. The liver and spleen were not felt. There was clubbing of the fingers and toes. Slight pitting edema of the ankles was present. There were several external hemorrhoids.

The laboratory data on admission were: Hinton reaction of the blood, negative; red blood cell count, 4,250,000; hemoglobin content, 12 Gm.; hematocrit value, 38.8 per cent; mean corpuscular volume, 91.3 cubic microns; mean corpuscular hemoglobin concentration, 31.2 per cent; mean corpuscular hemoglobin content, 28.3 micromicrograms, and reticulocyte count, 0.2 per cent. The white blood cell count was 6,200, with a differential count of 72 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes and 3 per cent monocytes. The urine was normal. The nonprotein nitrogen content of the blood was 26 mg. per hundred cubic centimeters. The fasting blood sugar level was 80 mg. and the serum total protein level 3.75 Gm. per hundred cubic centimeters. The corrected sedimentation rate (Wintrobe) was 0.1 mm. per minute. The stools were watery and light brown, and a guaiac test elicited a negative reaction.

Roentgen ray studies of the gastrointestinal tract revealed a normal stomach. The duodenum was somewhat dilated, and localized areas of dilatation with puddling of the barium and thickening of the mucosal folds were demonstrated in the upper portion of the jejunum. The lower part of the jejunum and the ileum exhibited fixed narrowing of the intestinal lumen, irregular and ragged mucosal markings and sharply localized round areas of dilatation (fig. 1). Intubation study of the upper portion of the jejunum demonstrated an abnormal motility pattern with low tone and frequent large waves tending to occlude the jejunal lumen. Gastric analysis on two occasions showed the presence of free hydrochloric acid in the fasting specimens. The result of an intravenous hippuric acid test was normal, 0.9 Gm. being excreted in one hour. The prothrombin content of the blood was 100 per cent. The cholesterol contents of the blood were 105 and 115 mg. per hundred cubic centimeters and the cholesterol ester contents 33 and 37 per cent. The alkaline phosphatase level was 3 units (King and Armstrong). The serum calcium levels were 8.0 and 8.2 mg. per hundred cubic centimeters; the inorganic phosphorus levels, 3.5 and 3.8 mg.; the diastase activity, 41 and 43 units (Somogyi), and the lipase activity, 0.93 units (Crandall and Cherry). The urinary diastase activity varied between 4 and 8 units (Wohlgemuth). The basal metabolic rate was —10 per cent on one occasion and —5 per cent on another. An electrocardiogram revealed normal conditions. The tuberculin test elicited negative reactions in dilutions of 1:10,000 and 1:1,000. Guinea pig inoculation with fecal material proved negative for tubercle bacilli.

Clinical Course.—The patient was afebrile and was allowed to walk about the ward as desired. His diet consisted of 300 to 400 Gm. of carbohydrate and about 100 Gm. each of protein and fat, amounting to an average daily intake of 2,500 to 3,000 calories. He received daily intramuscular injections of liver extract; later these were given twice weekly. He also took moderately large amounts of thiamine hydrochloride, nicotinic acid, riboflavin and vitamins A and D orally.

During the first month the patient showed no significant improvement, although the stools became semiformed and there was a slight gain in weight. However, the total proteins of the serum continued to decrease, reaching the exceptionally low level of 3.2 Gm. per hundred cubic centimeters with an albumin fraction of 1.7 Gm. Coincident with these changes there was a definite increase in the edema of the legs. It was evident that measures had to be taken to increase the blood proteins. Transfusions of blood plasma were considered, but the scarcity of plasma for civilian use, the tremendous amounts that would be required and the expense involved in such therapy prohibited this type of treatment. A considerable increase in dietary protein was incompatible with the patient's appetite, and it was considered questionable whether his abnormal intestine could handle an excess intake of protein. Since experimental [2] and clinical [3] reports have proved the efficacy of amino acids and protein hydrolysates administered parenterally and orally in maintaining a positive nitro-

2. (*a*) Nielsen, E. K.; Gerber, L. P., and Corley, R. C.: Retention of the Nitrogen of Amino Acids Administered Singly or in Mixtures to Dogs Fed Diets Low in Protein, Am. J. Physiol. **126**:215-222 (June) 1939. (*b*) Nielsen, E. K., and Corley, R. C.: Retention of the Nitrogen of Mixtures of Amino Acids Administered to Rats Fed Diets Low in Protein, ibid. **126**:223-228 (June) 1939. (*c*) Mueller, A. J.; Kemmerer, K. S.; Cox, W. M., Jr., and Barnes, S. T.: The Effect of Casein and a Casein Digest on Growth and Serum Protein Regeneration, J. Biol. Chem. **134**:573-583 (July) 1940. (*d*) Madden, S. C.; Zeldis, L. J.; Hengerer, A. D.; Miller, L. L.; Rowe, A. P.; Turner, A. P., and Whipple, G. H.: Casein Digests Parenterally Utilized to Form Blood Plasma Protein, J. Exper. Med. **73**: 727-743 (June) 1941. (*e*) Clark, D. E.; Brunschwig, A., and Corbin, N.: Utilization of Parenterally Administered Casein Digest for Synthesis of Proteins, Proc. Soc. Exper. Biol. & Med. **49**:282-285 (Feb.) 1942. (*f*) Elman, R.; Sachar, L. A.; Horwitz, A., and Wolff, H.: Regeneration of Serum Albumin with Hydrolyzed Protein in Chronic Hypoproteinemia Produced by Diet, Arch. Surg. **43**:1064-1070 (June) 1942.

3. Shohl, A. T.; Butler, A. M.; Blackfan, K. D., and MacLachlan, E.: Nitrogen Metabolism During the Oral and Parenteral Administration of the Amino Acids of Hydrolized Casein, J. Pediat. **15**:469-475 (Oct.) 1939. Farr, L. E.; Emerson, K., and Futcher, P. H.: The Comparative Nutritive Efficiency of Intravenous Amino Acid and Dietary Protein in Children with the Nephrotic Syndrome, ibid. **17**:595-614 (Nov.) 1940. Elman, R.: Parenteral Replacement of Protein with the Amino Acids of Hydrolized Casein, Ann. Surg. **112**:594-602 (Oct.) 1940. Messinger, W. J.: Serum Protein Regeneration Following Use of Amino Acids in Nephritis (Nephrotic Stage), Proc. Soc. Exper. Biol. & Med. **47**:281-284 (June) 1941. Brunschwig, A.; Clark, D. E., and Corbin, N.: Postoperative Nitrogen Loss and Studies on Parenteral Nitrogen Nutrition by Means of Casein Digest, Ann. Surg. **115**:1091-1102 (June) 1942. Altshuler, S. S.; Hensel, H. M.; Hecht, P., and Pursley, R.: Maintenance of Nitrogen Equilibrium by Intravenous Administration of Amino Acids, Arch. Int. Med. **70**:749-762 (Nov.) 1942. Altshuler, S. S.; Sahyun, M.; Schneider, H., and Satriano, D.: Clinical Use of Amino Acids for the Maintenance of Nitrogen Equilibrium, J. A. M. A. **121**:163-167 (Jan. 16) 1943. Mueller, A. J.; Fickas, D., and Cox, W. M., Jr.: Minimum Maintenance Requirement of an Enzymic Casein Hydrolysate, Bull. Johns Hopkins Hosp. **72**:110-115 (Feb.) 1943. Elman, R.: The Oral Use of the Amino Acids of Hydrolyzed Casein (Amigen) in Surgical Patients, Am. J. Digest. Dis. **10**:48-50 (Feb.) 1943.

gen balance and in some instances causing a regeneration of serum albumin, the patient was placed on a regimen of oral amino acids. The preparation used[4] was sufficiently concentrated so that he could take from 60 to 80 Gm. of amino acids daily. Another consideration which prompted the use of oral amino acids in preference to proteins was the fact that only the upper third of the small intestine was presumably capable of absorbing foods adequately. Under such circumstances, it seemed reasonable to administer a predigested form of protein material which would be available for absorption immediately on entering the duodenum and upper part of the jejunum.

In order to determine accurately the efficacy of administration of amino acids, it was necessary to carry out nitrogen balance studies.[5] As can be seen from figure 2, the exhibition of orally administered amino acids was followed by an increase in the positive nitrogen balance, with a rise in the serum total proteins to 4.94 Gm. per hundred cubic centimeters. However, this level was not maintained, and there was a gradual decline of the proteins to approximately 4 Gm. per hundred cubic centimeters. The peripheral edema disappeared three months after the start of the amino acid therapy. The patient's weight remained stationary long after the loss of the edema fluid, and it became evident that although he was still in positive nitrogen balance there was little further improvement in his clinical course.

Fig. 1.—Roentgenologic appearance of the small intestine. *A* and *B*, one hour roentgenograms taken on Dec. 11, 1942 and May 4, 1943, showing persistence of abnormalities. *C*, two hour roentgenogram taken on July 3, 1943, and *D*, three hour roentgenogram taken on Dec. 11, 1942, showing extensive distribution of abnormalities.

Analyses of his stools revealed that the daily excretion of nitrogen was only slightly above the upper limits of normal (table 1). That the amino acids were being utilized as well as absorbed was shown by analysis of the urine during a four day period; the excretion of amino acid nitrogen was small (table 2).

Steatorrhea was present, but the total amount of fat excreted, with the resultant caloric loss, was not significant (table 1). Since the lipase content of the duodenal juices was normal both in the fasting state and after pancreatic stimulation with acetylbetamethylcholine chloride (mecholyl) the moderate fecal loss of lipids was ascribed principally to curtailment in the absorbing surface of the small intestine. That absorption of fat-soluble vitamins occurred, although less than normal, was demonstrated by vitamin A tolerance tests, 250,000 U. S. P. units of vitamin A being used as the test dose (fig. 3). The fasting serum carotene values were also below normal, varying between 0.025 and 0.060 mg. per hundred cubic centimeters.

Oral dextrose tolerance tests showed that the patient was able to absorb dextrose rapidly from the small intestine, and the result of an intravenous dextrose tolerance test was within normal limits (fig. 4). Staining the stool with solution of iodine did not reveal an abnormal amount of undigested starch particles. However, on two successive occasions the pancreatic amylase was found to be 22.2 and 8.8 units (as grams of maltose) when the patient was fasting and 32.2 and 11.3 units after acetylbetamethylcholine chloride (mecholyl) was injected. The deficiency of pancreatic amylase suggested that the carbohydrates of more complex nature were probably not hydrolyzed sufficiently to permit normal absorption from the limited surface area of the non-diseased portions of small intestine. In order to increase the hydrolysis of starch in the stomach and upper part of the small intestine, a fungous amylase concentrate[6] was given in a dosage of 2 Gm. with each meal. With each dose of this concentrate 4 Gm. of calcium carbonate was taken in order to decrease the gastric acidity, the optimum p_H for the concentrate being between 5 and 6. Since the combination of orally administered amino acids and concentrated amylase produced nausea and a consequent decrease in food intake, the amino acids were discontinued after two weeks. With the amylase concentrate alone, however, progressive improvement was clearly evident (fig. 2).

During his thirty-eighth week in the hospital the patient was given amino acids[7] intravenously equivalent to 6 Gm. of nitrogen daily in order to determine whether an increase in the positive nitrogen balance would occur while he was still taking the concentrated amylase. However, there was no increase in nitrogen retention on this regimen.

An interesting observation was made in regard to the stool culture on Sabouraud's medium. Throughout the course prior to administration of the concentrated amylase, the stool cultures (and on one occasion a

4. Amino acids for oral use, derived from the enzymatic hydrolysis of casein, were furnished by Frederick Stearns & Company, Detroit.

5. The methods are described in the appendix.

6. The amylase concentrate (Neozyme) was supplied by Frederick Stearns & Company, Detroit. It is prepared from a selected species of the Aspergillus oryzae group. One 0.65 Gm. tablet will convert approximately 63 Gm. of potato starch into absorbable sugars at the end of five hours (in vitro).

7. The amino acids for parenteral use were furnished by Frederick Stearns & Company, Detroit.

culture of jejunal contents) showed a growth of Parasaccharomyces G (Monilia albicans). When stool cultures were made during the second week of therapy with the amylase concentrate, the cultures showed no growth and repeated cultures thereafter did not contain yeasts. However, cultures made five days after discontinuance of use of the concentrate again yielded Parasaccharomyces G.

COMMENT

Granulomatous jejunoileitis is an inflammatory disease of the small intestine of unknown cause. It appears to be closely related to regional enteritis but is characterized by a diffuse involvement of the jejunum as well as the ileum. The first extensive reports of a series of such cases were made by Crohn and Yunich [1a] and Sussman and Wachtel.[1b] Out of their experience with 200 cases of regional ileitis, Crohn and Yunich [1a] were able to segregate 17 examples of ileojejunitis.

The case we have reported fits well into the group of cases designated as jejunoileitis. The diarrhea, anorexia, loss of weight and low grade febrile course exhibited are among the outstanding symptoms of this disease. However, abdominal pain and cramps, prominent in the typical case, were not present. Clubbing of the fingers, frequently found in chronic malfunction of the intestine, was another feature exhibited by this patient. The severe hyperchromic macrocytic anemia, possibly due to a lack of extrinsic factor, responded well to parenteral injections of liver extract. Gastric achlorhydria was present during the acute stage of the disease, but gastric analyses later showed free hydrochloric acid in the fasting contents. The roentgenologic appearance of the gastrointestinal tract showed a striking similarity to that described in the reported cases. Although the patient made a pronounced clinical improvement, the abnormalities evident in the small intestinal pattern showed no significant changes during a year of observation.

Several features exhibited by this case suggested sprue, but it was excluded on the basis of the roentgenologic observations, the intestinal motility records, the dextrose tolerance tests, the

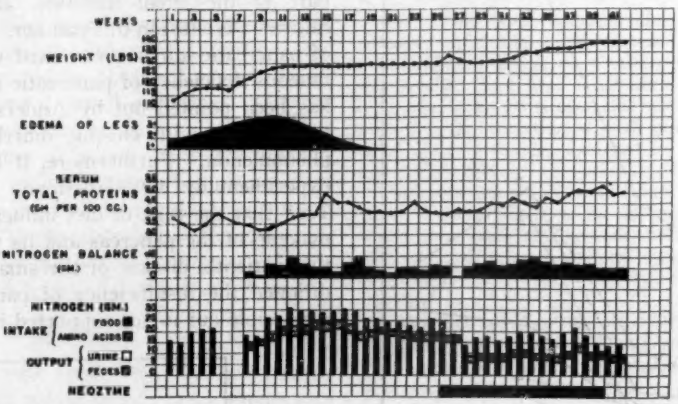


Fig. 2.—Clinical course and weekly nitrogen balances. The weekly nitrogen balances were obtained by averaging the daily balances determined during each week.

TABLE 1.—*Analyses of Feces for Nitrogen and Lipid Content*

	Wet Feces, Gm.	Dry Feces, Gm.	Fecal Nitrogen, Gm.	Fecal Fat, Gm.	Fat in Dry Feces, per Cent	Fat in Diet, Gm.	Dietary Fat Excreted, per Cent
Period I: Sept. 25, 26, 27, 1942	293.3	59.1	3.3	22.1	37	90	24
Period II: Oct. 14, 15, 16, 1942	309.9	63.9	4.0	19.5	30	90	22
Period III: Nov. 29, 30, and Dec. 1, 1942	229.0	44.0	2.75	14.4	32	90	16
Period IV: April 30 and May 1, 2, 1943	236.4	54.8	...	18.3	33	130	14
Normal values (average upper limits)	170.0	45.0	3.0	....	20	..	10

TABLE 2.—*Daily Urinary Excretion of Total Nitrogen, Urea Nitrogen and Amino Acid Nitrogen*

		Urea Nitrogen			Amino Acid Nitrogen	
Date	Total Urinary Nitrogen per 24 Hours, Gm.	Mg. per 100 Cc.	24 Hour Total, Gm.	Per Cent of Total Urinary Excretion of Nitrogen	Mg. per 100 Cc.	24 Hour Total, Gm.
11/27/42	14.28	728.2	9.46	66	18.0	0.23
11/28/42	14.88	666.6	10.66	71	17.0	0.27
11/29/42	18.94	787.0	15.16	75	20.2	0.36
11/30/42	20.00	702.0	14.04	70	20.2	0.44

vitamin A tolerance tests, the mild steatorrhea, the normal prothrombin levels of the blood and the clinical course. On the other hand, it is not impossible that a spruelike process was superimposed on the granulomatous disease at the time of the patient's entry to the Marine hospital.

The severe hypoproteinemia was undoubtedly aggravated by the eight day period of starvation, the prolonged diarrhea and the inadequate absorption of various components of the diet. The

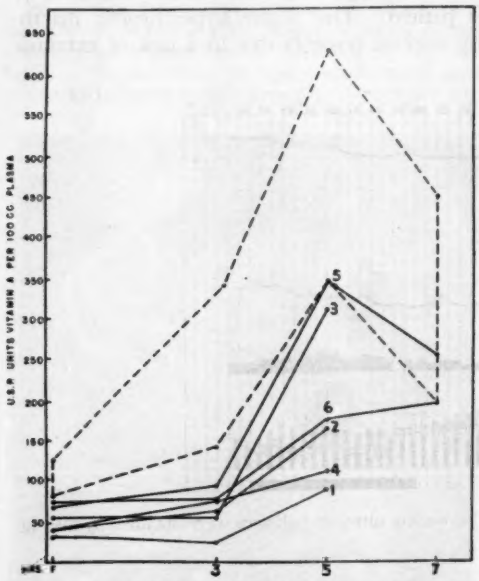


Fig. 3.—Vitamin A tolerance tests. The figure formed by the dotted lines encloses the normal values. The solid lines indicate results of tests on the patient: 1, on July 30, 1942; 2, on Sept. 17, 1942; 3, on Dec. 15, 1942; 4, on May 18, 1943; 5, on June 5, 1943; 6, on June 20, 1943.

oral administration of large amounts of amino acids in addition to the regular diet was instrumental in creating a significant positive nitrogen balance and resulted in a rise in the serum albumin with a partial correction of the hypoproteinemia. The large dose of hydrolyzed protein necessary to cause a regeneration of serum albumin has been demonstrated by Elman and associates[7] in dogs rendered hypoproteinemic by protein-deficient diets; 96.5 per cent of the nitrogen retained by the animals was utilized for the replenishment of the tissue proteins, while only about 3.5 per cent could be accounted for in the replenishment of serum albumin.

In spite of a diet apparently adequate in carbohydrate, fat and protein, the patient reached a state where there was no further increase in the serum proteins, even though administration of amino acids was continued. It seemed that although the amino acids were being absorbed from the gastrointestinal tract, they were possibly being deaminated and the non-nitrogenous residue used to furnish energy to the body. Since the patient was not gaining weight, this was fairly good evidence that the non-nitrogenous portion of the molecule was not being stored either as glycogen or as fat.

One reason that the patient's dietary intake was insufficient to take care of his metabolic requirements became apparent when an analysis of the duodenal juices revealed a deficiency of pancreatic amylase. Thus many of the more complex carbohydrates in his diet presumably were not hydrolyzed to dextrose in the upper part of the small intestine, and innumerable calories were lost in this manner. That deficiency of pancreatic amylase can exist without a simultaneous deficiency of pancreatic lipase or trypsin has been pointed out by Andersen,[8] who found that infants with chronic diarrhea exhibit this phenomenon. Furthermore, it has been shown experimentally by Grossman, Greengard and Ivy[9] that the type of diet influences the enzyme makeup of the pancreas and its secretion. That this patient's disease of the small intestine conditioned the insufficiency of pancreatic amylase is possible but is not supported by any evidence.

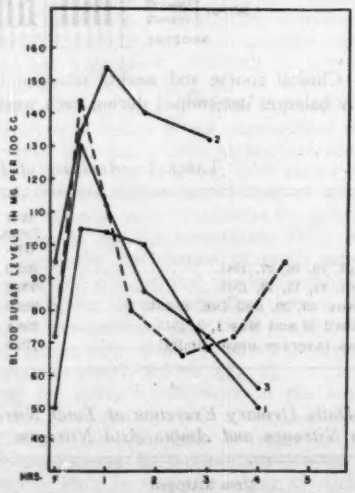


Fig. 4.—Dextrose tolerance tests. The solid lines represent results of oral tests: 1, on July 23, 1942; 2, on Aug. 5, 1942; 3, on June 4, 1943. The dotted line represents results of an intravenous test on Dec. 18, 1942.

The response to the amylase concentrate was striking. The immediate effect noticed was a de-

8. Andersen, D. H.: Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, Am. J. Dis. Child. **63**:643-658 (April) 1943.

9. Grossman, M. I.; Greengard, H., and Ivy, A. C.: The Effect of Dietary Composition on Pancreatic Enzymes, Am. J. Physiol. **138**:676-682 (March) 1943.

crease in abdominal distention and flatus. The appetite improved, more nitrogen was retained, serum albumin and total protein increased and a considerable gain in weight occurred. The disappearance of Monilia albicans (Parasaccharomyces G) from the stools while the patient was taking the amylase concentrate also suggests that the carbohydrates were broken down and absorbed rather than allowed to ferment in the intestine and so provide a favorable substrate for growth of these yeasts.

Serum vitamin A determinations showed extremely low fasting levels, but a progressive rise in these levels occurred after vitamin A was administered daily. The rise in the serum vitamin A level following a single large dose of vitamin A by mouth indicated that this fat-soluble vitamin could be absorbed even from an extensively damaged small intestine. On the other hand, the vitamin A tolerance tests yielded results which were definitely below the normal range (fig. 4), which is somewhat at variance with the results of Adlersberg and Sobotka,[10] who found that the average value of vitamin A tolerance tests carried out in 5 cases of jejunoileitis tended to fall within the normal range.

SUMMARY

A patient with extensive granulomatous jejunoileitis and pronounced hypoproteinemia was studied and the following observations made:

1. A deficiency in pancreatic amylase complicated the intestinal disease.

2. A positive nitrogen balance was easily established, but the hypoproteinemia and the weight responded only moderately to a high oral intake of proteins and amino acids.

3. Oral administration of a concentrated amylase was followed by a gain in weight and an increase in serum proteins, presumably by an increase in the breakdown and absorption of carbohydrates, which prevented the use of amino acids as a source of bodily energy.

4. The administration of the amylase appeared to inhibit the growth of Monilia albicans in the stools.

Dr. Chester Keefer and Dr. Richard Johnson made many suggestions regarding this study.

APPENDIX

Methods.—The food consumed by the patient was weighed by the dietitian and the protein, fat, carbohydrate and caloric value calculated from standard food tables. Twenty-four hour specimens of urine were collected daily and analyzed for total nitrogen. On several occasions specimens of urine were analyzed for amino acid nitrogen (Sahyun) [11] and urea nitrogen.

The stools were collected during four three day periods. The total lipid content was determined by acidifying and drying the total fecal output for a three day period. The dried feces were then powdered, and a 10 Gm. aliquot was extracted with ether in a Soxhlet apparatus and reextracted with purified benzine. The dried stools were also analyzed for total nitrogen content (Kjeldahl).

Determinations of the total serum proteins were made three times a week by the falling drop method, and occasionally these results were checked by the Kjeldahl method. Amino acid nitrogen levels of the blood were determined twice weekly according to the method of Sahyun.[11]

Vitamin A and carotene in the serum were determined according to the method of May and associates.[12]

The duodenal contents were collected by the method of Ågren and Lagerlöf.[13] The pancreatic amylase was determined according to the method of the same authors, and the pancreatic lipase, by the method of Crandall and Cherry.[14]

10. Adlersberg, D., and Sobotka, H.: Fat and Vitamin A Absorption in Sprue and Jejuno-Ileitis, Gastroenterology **1**:357-365 (April) 1943.

11. Sahyun, M.: The Determination of Amino Acid Nitrogen in the Blood and Urine: A Rapid Colorimetric Method, J. Lab. & Clin. Med. **24**:548-553 (Feb.) 1939.

12. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and Children, Am. J. Dis. Child. **59**:1167-1184 (June) 1940.

13. Ågren, G., and Lagerlöf, H.: The Pancreatic Secretion in Man After Intravenous Administration of Secretin, Acta med. Scandinav. **90**:1-29, 1936.

14. Crandall, L. A., Jr., and Cherry, I. S.: Studies on the Specificity and Behavior of Blood and Tissue Lipases, Proc. Soc. Exper. Biol. & Med. **28**:570-572 (March) 1931.

LATE CEREBRAL SEQUELAE OF RHEUMATIC FEVER

WALTER L. BRUETSCH, M.D.
INDIANAPOLIS

Until recently, rheumatic fever has been viewed as a disease taking place within a short period. The newer concepts, however, emphasize that the rheumatic infection may endure through the entire life of the patient.

Mental symptoms during acute rheumatic fever have been observed since the days of Benjamin Rush, founder of American psychiatry.[1]

Mental disease occurring within a period of several months following the acute stage, as the result of rheumatic cerebral involvement, has been described by Winkelman and Eckel.[2] A woman aged 33 had rheumatic fever. She recovered sufficiently to be able to do light house work. Several months later she began to have ideas of persecution, visual hallucinations and suicidal tendencies. When she died, shortly afterward, microscopic examination of the brain revealed proliferative endarteritis of the small cortical vessels and minute areas of partial and complete softening in the gray matter.

More recent neuropathologic studies[3] have directed attention to the fact that rheumatic involvement of the brain causing mental illness may occur many years after the acute stage of rheumatic fever, at a time when the person is otherwise enjoying good physical health.

This viewpoint had its inception in postmortem observations. In the necropsy service of the Central State Hospital, in Indianapolis, it was noted that patients with rheumatic lesions of the cardiac valves not infrequently had concomitant gross or microscopic changes in the brain and in other organs which, in the absence of other possible causative factors such as syphilis or arteriosclerosis, were interpreted as rheumatic alterations.

Several questions then presented themselves. First, what is the incidence of rheumatic infection among inmates of mental institutions? Secondly, what are the changes in the brain tissues of rheumatic patients who ultimately find their way into state hospitals? Thirdly, what are the psychiatric symptoms of these patients?

INCIDENCE OF RHEUMATIC FEVER AMONG PATIENTS WITH MENTAL DISEASE

An infallible sign of rheumatic fever in its inactive stage is rheumatic heart disease. In a group of 500 consecutive and unselected necropsies which I made on patients with mental disease, rheumatic cardiovalvular changes were noted in 4.4 per cent of the subjects. There was an additional 0.6 per cent of patients with rheumatic valvular lesions who had had positive reactions for syphilis. This made a total of 5 per cent of patients having rheumatic cardiac disease.

The figure of 5 per cent may be considered as representative of the prevalence of rheumatic heart disease in the population of the average mental disease hospital located in the same latitude. In this series of 500 necropsies no attempts were made to concentrate on rheumatic persons for the reason that in most instances a clinical diagnosis of rheumatic heart had not been made during life. Almost all patients with rheumatic cardiac disease in institutions for persons with mental illness are able to carry on ordinary activity without discomfort. Hence the presence of rheumatic infection remains unrecognized.

If the incidence of rheumatic valvular changes were compiled separately for the various types of psychoses, wide and significant differences would result. In a group of 171 patients with dementia

From the Central State Hospital.

Clinical Director, Central State Hospital; Clinical Professor of Psychiatry and Neurology, Indiana University School of Medicine.

1. Goodman, N. G.: Benjamin Rush, Physician and Citizen, 1746-1813, Philadelphia, University of Pennsylvania Press, 1934, p. 260. Haskell, R. H.: Mental Disturbances Associated with Acute Articular Rheumatism, Am. J. Insanity **71**:361 (Oct.) 1914. Winkelman, N. W., and Eckel, J. L.: The Brain in Acute Rheumatic Fever: Nonsuppurative Meningo-Encephalitis Rheumatica, Arch. Neurol. & Psychiat. **28**:844 (Oct.) 1932.

2. Winkelman, N. W., and Eckel, J. L.: Endarteritis of the Small Cortical Vessels in Severe Infections and Toxemias, Arch. Neurol. & Psychiat. **21**:863 (April) 1929.

3. Bruetsch, W. L.: The Histopathology of the Psychoses with Subacute Bacterial and Chronic Verrucose Rheumatic Endocarditis, Am. J. Psychiat. **95**:335 (Sept.) 1938. Bruetsch, W. L., and Bahr, M. A.: Chronic Rheumatic Brain Disease as a Factor in the Causation of Mental Illness, J. Indiana M. A. **32**:445 (Sept.) 1939. Bruetsch, W. L.: Chronic Rheumatic Brain Disease as a Possible Factor in the Causation of Some Cases of Dementia Praecox, Am. J. Psychiat. **97**:276 (Sept.) 1940; Rheumatic Endarteritis of Cerebral Vessels: Sequel of Rheumatic Fever, Tr. Am. Neurol. A. **68**:17, 1942.

paralytica, on whom necropsies were done, rheumatic valvular disease was present in only 1.7 per cent, while in 100 patients with schizophrenia the incidence was 9 per cent. Most of the schizophrenic patients had been inmates for many years, but they were not known to have suffered from active rheumatic fever during their stay in the institution.

The frequency of rheumatic infection among newly admitted patients with mental disease has also been the subject of a survey. Of 549 female patients admitted during the two year period of 1940 and 1941, 6.6 per cent had rheumatic heart disease. An additional 1.5 per cent had a definite history of rheumatic fever or of chorea, but no clinical signs of cardiac involvement. The total incidence of rheumatic infection in the female group was therefore 8.1 per cent.

During the same period 502 male patients were admitted. Of these only 1.6 per cent had a rheumatic heart. One per cent had a history of rheumatic fever or of chorea without cardiac symptoms. Thus a total of 2.6 per cent of male patients had rheumatic infection. The ratio between rheumatic men and women on this basis was approximately 1 : 3.

When these figures were compared with those for the general population, the difference assumed statistical significance. According to Hedley [4] the incidence of rheumatic heart disease in the United States is conservatively set at about 800,000 to 1,000,000 cases, or less than 1 per cent. The high prevalence of rheumatic cardiac disease among patients with mental disease in itself is highly suggestive that there might be a direct relationship between rheumatic fever and the mental symptoms. However, even before the rate of rheumatic heart disease among such patients had been established, postmortem observations had revealed the interesting fact that long-continued rheumatic infection involved not only the heart but the brain [5] and at times other organs, such as lungs,[5] kidneys [6] and spleen.

NATURE OF LATE CEREBRAL SEQUELAE OF RHEUMATIC FEVER

The involvement of the brain consisted most frequently of a recurrent rheumatic obliterating endarteritis, particularly of the small meningeal and cortical vessels, with subsequent gross or microscopic softenings in the cerebral cortex. This condition has been termed "rheumatic brain disease." A few patients had rheumatic meningoencephalitis. A third type of involvement was cerebral embolism occurring in patients with mitral stenosis during auricular fibrillation.

Rheumatic vascular lesions as a sequel of rheumatic fever were first described as occurring in the myocardium, by Krehl.[7] Later, Von Glahn and Pappenheimer,[8] Karsner and Bayless,[9] and Gross [10] demonstrated rheumatic endarteritis in the vessels of various internal organs. Von Sántha [11] observed similar changes in the cerebral vessels of a young patient with rheumatic chorea.

RHEUMATIC BRAIN DISEASE

The term rheumatic brain disease has been borrowed from internal medicine, which speaks of rheumatic heart disease in denoting both valvular and myocardial changes. In the same sense, the designation rheumatic brain disease comprises both the primary changes in the cerebral vessels and the manifold secondary lesions in the gray matter brought about by the proliferative endarteritis of the small meningeal and cortical vessels. There are also clinical similarities. Many persons with rheumatic heart disease are well and unaware of the cardiac condition until an incidental physical examination reveals a heart murmur. Similarly, most patients with mental disease who have rheumatic brain disease appear physically and neurologically well, a heart murmur and a history of previous rheumatic fever giving the only clue to the etiologic background of the mental illness.

The sequence of events in a few clinically and anatomically well observed cases will be given.

At the age of 6 years the patient had chorea. The first mental symptoms appeared at 18, when she became seclusive and expressed delusions of persecution. On her admission to the state hospital, physical examination revealed nothing significant except a mitral murmur, which was not properly interpreted. The diagnosis was dementia precox. At 54 years of age she died of rheumatic mitral stenosis. Histologic examination of the brain revealed meningeal vessels with signs of old and recent obliterating endarteritis, associated with microscopic areas of incomplete softenings in the cortex. In the kidneys old infarctions were present.

4. Hedley, O. F.: Rheumatic Heart Disease: A National Health Problem, Proc. A. Life Insur. M. Dir. America (1938) **25**:163, 1939.

5. Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation: Rheumatism of the Pulmonary Arteries, Arch. Int. Med. **56**:1190 (Dec.) 1935.

6. Fahr, T.: Kurze Beiträge zur Frage der Nephrosklerose, Deutsches Arch. f. klin. Med. **134**:366, 1920.

7. Krehl, L.: Beitrag zur Pathologie der Herzklappenfehler, Deutsches Arch. f. klin. Med. **46**:454, 1890.

8. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, Am. J. Path. **2**:235 (May) 1926.

9. Karsner, H. T., and Bayless, F.: Coronary Arteries in Rheumatic Fever, Am. Heart J. **9**:557 (June) 1934.

10. Gross, L.; Kugel, M. A., and Epstein, E. Z.: Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, Am. J. Path. **11**:253 (March) 1935.

11. von Sántha, K.: Ueber Gefässveränderungen im Zentralnervensystem bei Chorea rheumatica, Virchows Arch. f. path. Anat. **287**:405, 1932.

In other words, rheumatic lesions of many years' duration were observed side by side with more recent changes. This suggests that rheumatic fever in a chronic form had been present since the age of 6 years, when the patient had chorea, and that the infection had continued to be mildly active until her death, at 54.

In another patient, aged 39, described as having a well adjusted personality, there developed a schizophrenic psychosis with many ideas of persecution. There was no history of rheumatic fever or of chorea, but her mother had suffered from rheumatism. The heart was of normal size. Cardiac murmurs were not heard or, if audible, were missed by the examiner. Five months after the onset of the psychosis the patient committed suicide by hanging. The brain was grossly normal. However, throughout the cortex of the entire brain microscopic areas of softenings were observed, which at times had progressed into minute cysts extending over several cell layers. The changes in the gray matter were dependent on diseased cortical vessels. On the mitral valve was recurrent rheumatic endocarditis. In the kidneys, spleen, liver and pancreas a few rheumatic endarteritic vessels were noted.

Since rheumatic brain disease in itself is not a fatal condition, most of the patients live out their span of life in an institution for persons mentally ill unless they die prematurely of mitral stenosis or some intercurrent disease or as a result of an accident. It may be argued that the changes in the brain are not related to the mental symptoms and are a later development in the patient's life. In this instance, however, the unusual opportunity had presented itself to study the early manifestations of rheumatic involvement of the brain, which were coincident with the onset of the psychosis.

In these 2 patients the cerebral process had produced the clinical picture of schizophrenia. Modern psychiatry has viewed schizophrenia as a mere maladjustment of the person to the environment. Singer,[12] however, expressed the belief that in some cases a disease process had occurred, and he classified such cases as instances of "schizophrenia, organic type." In those cases in which the illness was obviously a reaction to the environment, the condition was termed "schizophrenia, psychogenic type."

The mental picture of the patients with rheumatic brain disease does not show any characteristic psychopathologic content. The form of the psychosis is determined by the personality and also by the age at which the involvement of the brain occurs.

In 2 instances rheumatic fever had produced cerebral damage in childhood resulting in mental deficiency. When the patients, who also showed later psychotic manifestations, died at the ages of 43 and 46 respectively of mitral stenosis, obliterating vascular disease of varied age was present. In 1 patient this had produced gross cortical infarctions in the left frontal lobe.

Milder types of mental abnormalities in children following Sydenham's chorea have long been known. At the Emma Pendleton Bradley Home,[13] a hospital which limits its activities to children with emotional disturbances, the number of behavior disorders following rheumatic chorea is next in frequency to postencephalitic personality change.

If the rheumatic involvement of the brain occurs later in life, a psychiatric symptom complex characteristic of that period will be produced.

A woman who had had rheumatic fever at 21 showed mental symptoms resembling involutional melancholia at the age of 51. Seven years previously she had had a slight stroke which left no obvious residue. On her admission to the hospital there was chronic rheumatoid arthritis of both hands and knees. A systolic blow in the mitral and aortic area was heard. The blood pressure was 145 systolic and 80 diastolic. The patient died at the age of 60 of tuberculous spondylitis. In the brain were infarcted convolutions in addition to numerous minute areas of incomplete cortical softenings. There was no arteriosclerosis, and the cerebral process was interpreted as rheumatic. Under the microscope the mitral and aortic valves revealed old and recent rheumatic alterations.

Prior to death this patient was considered as suffering from involutional melancholia on a psychologic basis. Since rheumatic heart disease and mental illness affect an appreciable proportion of the population, psychoses will develop in persons with rheumatic cardiac disease in whom the rheumatic infection does not produce changes in the brain and is unrelated to the mental symptoms. Unfortunately, the clinical picture gives no clue as to whether one is dealing with an organic psychosis or with a mental disturbance on a psychogenic background.

The question has been raised whether a biopsy on the brain would be of value. The rheumatic changes in the brain are evident in some areas and are absent in others. It is characteristic of rheumatic endarteritis that not all vessels are included in the obliterating process and that only short segments are diseased. Postmortem experience has shown that rheumatic lesions are present in only about one half of the brain blocks examined. While a biopsy disclosing rheumatic changes would be proof of the existence of cerebral involvement, a negative result would not exclude the presence of rheumatic brain disease.

12. Sherman, I. C., and Broder, S. B.: Dr. H. Douglas Singer's Concept of the Psychoses, Arch. Neurol. & Psychiat. 49:732 (May) 1943.

13. Achievements of the First Ten Years, 1931-1941, Emma Pendleton Bradley Home, East Providence, R. I., 1941, p. 11.

Necropsy experience, however, points to the fact that in mentally ill patients with rheumatic heart disease coexisting lesions of the brain are frequent. In only 1 of 30 patients who had rheumatic valvulitis was the brain free of changes. In 15 patients there were gross cortical infarctions, and in the remaining 14 the cerebral changes consisted of microscopic areas of complete and partial softenings in the cortex. With a few exceptions the basal ganglions and other structures of the brain were normal.

Most of this work had been done before electroencephalography had become practical. It will be left for the future to establish possible correlations between electroencephalographic abnormalities and rheumatic cortical lesions.

RHEUMATIC ENCEPHALITIS

Meningoencephalitis in patients with rheumatic cardiovalvular disease is of infrequent occurrence. Only 2 instances were observed over a ten year period.

One of these patients was a 47 year old woman, who six weeks prior to admission suddenly became disturbed and required restraint. She talked continually and incoherently, refusing food and water. On admission to the hospital, two days before her death, the patient was delirious and had a temperature of 104 F. The heart sounds were distant. There were no murmurs. The joints were normal. The husband related later that his wife had suffered in previous years from articular rheumatism. Autopsy revealed on an otherwise normal mitral valve a single firm verrucous wart. In the spleen and the kidneys were old and new infarctions. The brain was swollen, and there was fresh softening of the left temporal lobe, due to massive round cell accumulations. Throughout the white matter of the entire brain, including the midbrain and pons, but less in the cortex, were perivascular infiltrations. In the pia-arachnoid were a few localized areas with lymphocytes and plasma cells. Cerebral arteriosclerosis and gross and microscopic signs of syphilis of the aorta and other organs were absent.

RHEUMATIC CEREBRAL EMBOLISM

At the beginning of this study it was assumed that the cortical damage which has been termed rheumatic brain disease was caused by minute emboli detaching themselves from the cardiac valves. This thought proved erroneous, and the source of the vascular occlusions was found to have its origin in local proliferation of the intima. Furthermore, in studying histologically rheumatic cardiac valves, it could easily be seen that embolic material will not detach itself readily from fibrous verrucae.

Rheumatic cerebral embolism develops most frequently in cases of mitral stenosis during auricular fibrillation, the soft newly formed mural thrombi furnishing the material for emboli. The following case will illustrate this type of cerebral involvement.

In a 62 year old woman with a history of repeated attacks of auricular fibrillation in the past year there developed a progressing mental deterioration giving the impression of senile psychosis. At the age of 12 she had had rheumatic fever. There was a mild recurrence of articular symptoms when she was 52. She died of mitral stenosis ten days after admission to the institution. In the brain was a large infarction involving the left occipital-parietal region and extending into the upper temporal convolutions. The cerebral vessels were free of atherosclerotic plaques. No signs of intimal proliferation were observed in these vessels, and the large infarction was interpreted to be the result of an embolic manifestation during one of the attacks of auricular fibrillation in the year preceding the patient's death.

RHEUMATIC OBLITERATING ENDARTERITIS IN OTHER NEUROLOGIC CONDITIONS

Rheumatic disease of the vessels of the central nervous system may prove the cause of a number of obscure neurologic conditions in patients with rheumatic heart disease.

A paralytic stroke occurring in middle life has usually been associated with syphilis, even in the absence of positive serologic reactions. If in a young person an unexplained hemiplegia develops and physical examination reveals a mitral or aortic murmur, the correct interpretation of the neurologic symptoms may be on the basis of rheumatic vascular occlusion of one of the larger vessels supplying the internal capsule.

Epileptic seizures appearing in the years following an attack of rheumatic fever or chorea have definitely been traced to rheumatic obliteration of cerebral vessels.[14] Foster[15] has shown that the incidence of convulsive seizures in patients with rheumatic heart disease is from two and a half to seven times higher than in the average population.

A diagnostic problem belonging under this heading has recently been reported.[16] A patient aged 45 was hospitalized with symptoms of epidemic encephalitis. A murmur over the mitral and aortic area with generalized cardiac enlargement was noted, but this observation was not utilized in the interpretation of the clinical picture. Necropsy revealed multiple areas of fresh endarteritic or embolic softenings in the midbrain, which were responsible for the symptoms suggesting epidemic encephalitis. There was aortic stenosis, and on the mitral valve were extensive rheumatic vegetations.

14. Bruetsch, W. L.: Rheumatic Epilepsy: Sequel of Rheumatic Fever, Am. J. Psychiat. **98**:727 (March) 1942.

15. Foster, D. B.: Association Between Convulsive Seizures and Rheumatic Heart Disease, Arch. Neurol. & Psychiat. **47**:254 (Feb.) 1942.

16. Alexander, L.: The Diseases of the Basal Ganglia, A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:454, 1942.

If encephalitic symptoms appear in a person with rheumatic heart disease, the thought should always be kept in mind that the patient may be suffering from rheumatic cerebral involvement of an encephalitic, endarteritic or embolic type. This is true especially if there is no epidemic and other types of encephalitis can be excluded.

CONTINUITY OF RHEUMATIC FEVER

The study has brought out the continuity of rheumatic fever in a chronic form throughout the entire lifetime of the patient and in the absence of any symptoms which are generally regarded as evidence of activity. In many instances mild activity could be demonstrated in the tissue of the mitral or aortic valve, consisting of loosely arranged foci of round cells, of occasional fibroblasts in the stage of cell division or of minute collections of fibrin along the closing border which were undergoing organization. Likewise, in the brain and in other organs vascular changes of varied age could be observed, which revealed that the rheumatic process was recurrent and was still slightly active, although the original attack of rheumatic fever had taken place sometimes several decades before. It is evident, then, that the term "inactive rheumatic fever," which of late has been used for rheumatic conditions without obvious clinical symptoms, should be employed with caution.

SUMMARY

A late sequel of rheumatic fever is obliterating endarteritis, which usually develops while the patient is otherwise in good health. If the vascular process involves the small meningeal and cortical vessels, gross and microscopic infarctions in the gray matter of the brain will result, producing a variety of mental symptoms. This type of cerebral involvement has been termed "rheumatic brain disease." It represents a chronic infectious process in the same sense as rheumatic heart disease.

Although widespread and clinically manifest obliterating arteritis seems to occur in only a small number of patients with rheumatic heart disease, the possibility of the development of rheumatic endarteritis in such persons appears to be ever present.

Rheumatic fever in the form of this late cerebral sequel has been found to be an important factor in the causation of mental illness. The fact that rheumatic heart disease is several times more frequent among mentally ill patients than in persons of the general population emphasizes this contention.

Other late cerebral sequelae of rheumatic fever are rheumatic encephalitis and cerebral embolism, the latter occurring most often during auricular fibrillation in patients with mitral stenosis.

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1943

CONGER WILLIAMS, M.D.

WITH THE EDITORIAL ASSISTANCE OF PAUL D. WHITE, M.D.

BOSTON

Despite the war, special interest has continued and work has been done in certain fields of cardiovascular disease, particularly in electrocardiography, congenital defects, arrhythmias and hypertension. There are many problems relating to cardiovascular disease in wartime, which are of significance but which have not been published because of censorship or other restrictions. For this reason, this paper is mostly concerned with the advances made in civilian practice.

ANATOMY, PHYSIOLOGY AND METHODS

Observations on velocity of blood flow have been used for a long time to assist in the diagnosis of heart failure, to help judge the severity of the failure and to evaluate the results of therapy. Unfortunately many of the methods in current use require intelligent cooperation on the part of the patient to produce a good end point.

Esser and Berliner [1] devised a test to show variations in circulation time in the individual patient, using saccharin. Sixty patients were used in the experiment, and the circulation time was first measured. After one hour the determination was repeated, with the same dose of the same drug. In only 6 cases were the results identical. In the remaining 54 the figures disagreed by values from 1 per cent to 143 per cent of the original. At first glance it might be thought that this could be accounted for by assuming that the patient was better prepared to judge the end point in the second experiment by virtue of his experience with the first. However, the time in the second test was prolonged as often as it was shortened in comparison with the first. About half the patients were tested under basal conditions, and in this group the results were somewhat better than in the total number, suggesting that the period of adjustment to rest between the two tests might have had something to do with the variable result. The authors concluded that the saccharine test for circulation time should be performed under basal conditions and that it should not be relied on to test the progress or course of the patient with cardiac disease.

Koster and Sarnoff [2] used theophylline ethylenediamine in a dose of 1 cc. of solution (0.24 Gm.) intravenously to measure the circulation time, taking as an end point the involuntary respiratory gasp. They reported a sharp end point, with only 1 failure in 72 cases. This is an objective method which does not depend on the variable subjective reactions of the patient.

Lange and Boyd [3] stress the need for a purely objective measurement of circulation time. They recommend an improvement on a technic previously reported by the first author, using fluorescein intravenously. A light source of mercury vapor with a purple glass filter is directed against the lips of the patient, which acquire a greenish yellow hue when the substance reaches the capillaries in the lips. The end points they obtained were very sharp, and repeat determinations of circulation time showed excellent results, the values never differing more than three seconds. In the majority of cases the difference was two seconds or less. They included observations on normal persons and on patients with heart disease, bronchial asthma and hyperthyroidism.

Gross [4] has extended the usual measurements of vital capacity to include other functions of respiration which are said to have more diagnostic significance than the vital capacity alone. He timed the minimum duration of the expiration which represented vital capacity and then calculated the velocity of expiration by dividing the vital capacity by the minimum duration of expiration. A third function, expiratory pres-

From the Cardiac Laboratory of the Massachusetts General Hospital.

1. Esser, K. H., and Berliner K.: Duplicate Measurements of Circulation Time Made with the Saccharine Method, Ann. Int. Med. **19**:64, 1943.

2. Koster, H., and Sarnoff, S. J.: Circulation Time: A Review of Previous Methods and the Introduction of Aminophyllin as a New Agent, J. Lab. & Clin. Med. **28**:812, 1943.

3. Lange, K., and Boyd, L. J.: Objective Methods to Determine the Speed of Blood Flow and Their Results (Fluorescein and Acetylene), Am. J. M. Sc. **206**:438, 1943.

4. Gross, D.: Investigations Concerning Vital Capacity, Am. Heart J. **25**:335, 1943.

sure, was measured by having the patient breathe into a tube connected with a mercury blood pressure manometer. These quantities were then determined on 30 normal persons of the same age, 10 patients with congestive heart failure and 10 patients with pulmonary disease, including emphysema and asthma. He also studied a miscellaneous group of 10 patients having either pulmonary or cardiac disease but not both. There was no relation between the vital capacity and the expiratory pressure. In those subjects who showed decrease in vital capacity due predominantly to cardiac disease the expiratory time was prolonged, the velocity of the spirometric expiration was decreased and, most significant, the expiratory pressure was decreased greatly, typically falling below half of the standard value.

Measurements on patients with pulmonary disease, on the other hand, showed considerable prolongation of the expiratory time, a distinct decrease in velocity of expiration and no significant change in expiratory pressure. One group of patients with normal vital capacity showed abnormal expiratory pressure or expiratory velocity. All of these had cardiac or pulmonary disease. For these patients the new measurements were helpful in uncovering apparent abnormalities not evident in the measurement of vital capacity. These methods may be of some value in studying the physiologic basis of disturbances of respiration in cardiac and pulmonary disease.

Warren and Stead [5] studied the effect of the accumulation of blood in the extremities on venous pressure in 6 normal subjects. They applied venous tourniquets at a pressure of 85 mm. of mercury to the thighs, producing an average fall of venous pressure in the external jugular vein of 53 mm. of water and in the antecubital vein of 23 mm. They explain this difference by pointing out that veins of the arms tend to collapse when venous pressure is lowered and that further lowering of pressure proximal to the collapse produces no further decrease in venous pressure in the distal part of the vein. In advanced cardiac failure, when the venous bed is already distended by greatly increased venous pressure, the veins cannot be distended much farther and therefore the value of application of tourniquets may be small. Also, in the presence of marked edema of the extremities the high tissue pressure may prevent the accumulation of large amounts of blood in the veins.

5. Warren, J. V., and Stead, E. A., Jr.: Effect of the Accumulation of Blood in the Extremities on Venous Pressure in Normal Subjects, Am. J. M. Sc. **205**:501, 1943.

May [6] describes a new and simple clinical method of measuring venous pressure in the patient with cardiac disease. With the subject in the upright position, the veins of the under surface of the tongue are observed. Since the veins in the tongue lie about 200 mm. above the right auricle in the average patient, they will be collapsed with the subject erect unless the venous pressure is abnormally high, that is, greater than 200 mm., in which case distention or venous pulsation has been noted.

Bartlett and Carter [7] advocate the routine use of electrocardiography and phonocardiography as a screening process in the detection of cardiovascular disease. They suggest that such methods might be valuable as applied to large numbers of persons in much the same way that the tuberculin test and roentgen examination are used to separate tuberculous from noninfected persons. They imply that the advantages to be gained lie in the ability to examine large numbers with routine methods which can be carried out by technicians. They also imply that such methods will often reveal abnormalities not evident to a skilled observer on physical examination.

The present day emphasis on primary value of mechanical aid, in auscultation especially, is unfortunate. Not only does it overlook the fact that the detection of murmurs by phonocardiography often requires the proper placing and selection of microphones, but it gives a false sense of security in relying on these aids. Certainly the value of electrocardiography as a screening process, especially for young persons, is slight, and it is well known that considerable persistence may be required to record by mechanical methods auscultatory abnormalities obvious to trained ears.

ARRHYTHMIAS

In the past the occurrence of auriculoventricular block in the presence of auricular paroxysmal tachycardia has been considered a rather rare event. In a comprehensive article Barker, Wilson, Johnston, and Wishart [8] review 17 previously reported cases of this phenomenon and add 8 new cases. They state that the abnormality may occur at any age in persons with organic

6. May, A. M.: The Tongue Sign for High Venous Pressure, Am. Heart J. **26**:495, 1943.

7. Bartlett, W. M., and Carter, J. B.: Combined Electrocardiography, Stethography and Cardioscopy in the Early Diagnosis of Heart Disease, Ann. Int. Med. **19**:271, 1943.

8. Barker, P. S.; Wilson, F. N.; Johnston, F. D., and Wishart, S. W.: Auricular Paroxysmal Tachycardia with Auriculoventricular Block, Am. Heart J. **25**:765, 1943.

heart disease or with otherwise normal hearts. In 60 per cent of their cases the P waves were upright, which suggested an origin near the sinoauricular node. They believe that auriculoventricular block is more likely to develop when the arrhythmia originates near the sinoauricular node than when its origin is near the auriculoventricular node. This auricular paroxysmal tachycardia with auricular block is considered somewhat different from the common types of auricular paroxysmal tachycardia and bears some resemblance to auricular flutter in the following characteristics: partial auriculoventricular block, long duration, slowing of the auricular rate with quinidine, conversion to auricular fibrillation in a few cases with large amounts of digitalis, increase in the degree of auriculoventricular block with pressure on the carotid sinus but rare conversion to normal rhythm, and lack of response to mecholyl. It differs from flutter in that the auricular deflections are always separated by an isoelectric interval in the electrocardiogram, which never occurs in flutter, although esophageal leads may sometimes be necessary to demonstrate the continuous oscillation of the circus wave in flutter. They believe that most of the features of this type of paroxysmal tachycardia can be accounted for by a circus rhythm involving either the sinoauricular or the auriculoventricular node.

In another article, which represents an extension and elaboration of these ideas, Barker, Johnston and Wilson [9] report a study of the electrocardiograms of 100 patients with auricular paroxysmal tachycardia. Ten pjatients had a slight irregularity characterized by alternation in the lengths of the cycles. The contours of the auricular deflections were uniform, and the authors believe this requires that "the longer and shorter paths be close together throughout their courses, or at least in that part which lies in auricular muscle, which makes a major contribution to P deflection." The variation observed was often considerable, frequently 0.05 second and often as great as 0.1 second. They suggest that alternation of cycle length may be accounted for if it is supposed that paroxysmal auricular tachycardia is caused by a circus rhythm involving the sinoauricular or the auriculoventricular node. "There is evidence that tissues of both these nodes have a relatively long refractory period, and that conduction in the latter, at least, is relatively slow. Thus a relatively slight alternation in the length of the path through one of the nodes could cause a considerable change in duration of the cycle without modifying the form of auricular deflection."

Barker, Wilson and Johnston [10] in still another article on the mechanism of auricular paroxysmal tachycardia present a summary of their own ideas and those of others pertaining to the physiologic characteristics of this mechanism. They believe that the underlying mechanism of auricular paroxysmal tachycardia is a circus rhythm in the auricles, the path of which passes through one of the specialized auricular nodes. In support of this belief they list the following facts: There is evidence to show that the action of events outside the heart on the arrhythmia is concentrated on the specialized auricular nodes. Slowing of the auricular rate and termination of paroxysms are produced by vagal stimulation and by digitalis, and acceleration of the rate, by exercise. As previously stated, auriculoventricular block in paroxysmal tachycardia is rare in cases in which there are inverted auricular deflections.

Further support for the theory of circus rhythm is found in the abrupt nature of the onset and termination of attacks, the remarkable stability of the rate, slowing of the auricular rate and termination of the attacks by quinidine. The occasional alternation in cycle length, as mentioned in the previous article, is another point in support of the theory. They mention several exceptions which cannot be explained by circus rhythm. In rare cases the rate slows gradually to normal instead of terminating abruptly. It is considered that these probably are not examples of true auricular paroxysmal tachycardia but rather represent an unusual and persistent type of sinus tachycardia. Also, auricular deflections of varying form are sometimes seen in auricular tachycardia, which suggests different origin of impulses in different regions of the auricles.

Another rare type of this disorder is that which shows an inverted P wave in lead I and an upright P wave in leads II and III. It is believed that the form of the deflections suggests an origin in the upper part of the left atrium far from the nodes of specialized tissue. But such cases are decidedly uncommon. Only 2 were encountered among 100 unselected cases studied.

Decherd, Herrmann and Schwab [11] collected 40 cases of paroxysmal auricular tachycardia in which there was auriculoventricular block. Only cases in which dropped ventricular premature

9. Barker, P. S.; Johnston, F. D., and Wilson, F. N.: Auricular Paroxysmal Tachycardia with Alternation of Cycle Length, Am. Heart J. **25**:799, 1943.

10. Barker, P. S.; Wilson, F. N., and Johnston, F. D.: The Mechanism of Auricular Paroxysmal Tachycardia, Am. Heart J. **26**:435, 1943.

11. Decherd, G. M.; Herrmann, G. R., and Schwab, E. H.: Paroxysmal Supraventricular Tachycardia with A-V Block, Am. Heart J. **26**:446, 1943.

beats appeared were included. A prolonged P-R interval alone was not considered of sufficient importance to warrant inclusion of the case in the series. The cases were selected from 102 instances of supraventricular paroxysmal tachycardia of varying duration, an incidence of about one third. The authors explain this high incidence by stating the fact that most of the records were obtained from patients who had been hospitalized for cardiac disease. Only 2 had normal hearts, and, in addition, most patients had received digitalis and quinidine. The form of the deflection of the P wave, which would have been of some interest in the light of the data presented in the articles just preceding, is not described specifically.

Cooke and White [12] prepared a study of ventricular paroxysmal tachycardia comprising 27 cases. This article was summarized in detail in last year's review on "Diseases of the Heart" published in this journal.[13]

Williams and Ellis [14] report 36 cases of the same abnormality collected from a series of 60,000 electrocardiograms. In all but 1 case organic heart disease was present. Toxicity due to digitalis was found to be the most frequent precipitating factor, with myocardial infarction next. It is emphasized again that the prognosis in such cases is that of the underlying heart disease. The use of chest leads as a valuable aid in the diagnosis of ventricular tachycardia is described. The chest electrode was placed in the third right interspace at the sternal border, and in several instances P waves which could not be seen in the standard leads were demonstrated. Since the diagnosis often depends on establishing the presence of an independent auricular rhythm, this procedure is considered to be of some value, except in cases of coexisting auricular fibrillation or auricular standstill.

Edeiken [15] adds 2 cases of extreme tachycardia with a ventricular rate of 300 or more to the 15 cases already reported in the literature. Probably in only 1 of these cases was the abnormality of ventricular origin. It was thought that treatment probably had little effect on the arrhythmias. Three of the infant patients died during a paroxysm.

12. Cooke, W. T., and White, P. D.: Paroxysmal Ventricular Tachycardia, Brit. Heart J. **5**:33, 1943.

13. Graybiel, A., and White, P. D.: Diseases of the Heart: A Review of Significant Contributions Made During 1942, Arch. Int. Med. **71**:713 (May) 1943.

14. Williams, C., and Ellis, L. B.: Ventricular Tachycardia, Arch. Int. Med. **71**:137 (Feb.) 1943.

15. Edeiken, J.: Extreme Tachycardia with Report of Non-Fatal Paroxysms Following Myocardial Infarction, Am. J. M. Sc. **205**:52, 1943.

TREATMENT OF ARRHYTHMIAS

Sampson, Alberton and Kondo [16] present a good review of the present knowledge of the relation of administration of digitalis to potassium balance in the heart and add some observations of their own. In experiments carried out on a number of patients they showed that ectopic beats caused by digitalis could be abolished in every instance by oral administration of a potassium salt (potassium acetate in a dose of 5 to 10 Gm.). They also studied the fasting potassium level of the blood serum and showed that there was no relation between that quantity and the presence or absence of ectopic ventricular beats. Furthermore, in a study of the curves of rise and fall of serum potassium in relation to the oral administration of potassium acetate, no significant differences occurred during administration of digitalis, even with toxic doses. Also, in many instances the serum potassium remained at fasting levels for a long period before ectopic beats again appeared. They suggested that lack of quantitative relationship between the serum potassium level and the occurrence of ectopic beats suggested fixation of potassium to cardiac muscle or alteration of the state of that muscle by potassium. It was believed that these findings offered positive evidence that the disturbance of potassium balance in the heart muscle is related to administration of digitalis.

Boyd and Scherf [17] employed intravenous injections of magnesium sulfate in the treatment of 11 patients with paroxysmal arrhythmia, who included 2 patients with ventricular tachycardia, 8 with auricular tachycardia and 1 with auricular flutter. Injection of a 10 per cent solution of the drug was beneficial in three out of eight attacks, while a 20 per cent solution succeeded in eight out of eight attacks. The auricular flutter was not affected. As possible toxic consequences of the injections the authors cited increase of the PR interval and ventricular extrasystoles appearing for a short time following. No serious reactions were observed. However, the authors hesitate to use the drug in the presence of extreme myocardial damage, serious disturbances in auriculoventricular conduction or gallop rhythm.

Sagall, Horn and Riseman [18] studied the effects of oral and intramuscular administration of

16. Sampson, J. J.; Alberton, E. C., and Kondo, B.: The Effect on Man of Potassium Administration in Relation to Digitalis Glycosides, with Special Reference to Blood Serum Potassium, the Electrocardiogram and Ectopic Beats, Am. Heart J. **26**:164, 1943.

17. Boyd, L. J., and Scherf, D.: Magnesium Sulfate in Paroxysmal Tachycardia, Am. J. M. Sc. **206**:43, 1943.

18. Sagall, E. L.; Horn, C. D., and Riseman, J. E. F.: Studies on the Action of Quinidine in Man, Arch. Int. Med. **71**:460 (April) 1943.

quinidine on 16 persons, 11 of whom were normal. First a control electrocardiogram was taken; then more tracings were taken at fifteen minute intervals for one hour, with subsequent tracings during the ensuing eight to fifteen hours at less frequent intervals. At the end of twenty-four hours a final record was taken. A number of methods of giving the drug were used. In every case the effect of the drug was evidenced by a prolongation of the QT interval, which was much more constant than the effect on the T wave. Shortly after the administration of a single dose of quinidine or quinine by mouth, the prolongation of the QT interval became maximum in one-half hour to three hours, was maintained in slightly lesser degree for three to five hours and was no longer evident at the end of twenty-four hours. From these studies they concluded that quinine was much less effective than quinidine and that larger doses of the latter caused production of a more prolonged effect and were evident sooner but did not alter the time of maximum response. The response to quinidine given by the intramuscular route was much more prompt and the magnitude of effect was slightly greater but the duration varied little from that observed with the oral method. They concluded that in the treatment of acute arrhythmias a dose should be given every two to two and a half hours.

In another article, Sturnick, Riseman and Sagall [19] report on the clinical use of a soluble quinidine preparation suitable for intramuscular injection. The mixture contains 0.15 Gm. per cubic centimeter of quinidine, with a similar amount of antipyrine and 0.2 Gm. of urea. The latter two drugs increase the solubility of the quinidine but have no other effect. The authors state that a search of the literature revealed no preparation of quinidine in sufficient concentration to warrant intramuscular use; the formula just given was obtained from the Cinchona Institute.

Their clinical observations were carried out on persons with a representative group of cardiac arrhythmias, including both auricular and ventricular tachycardias. From the results of their work the following dosage is recommended. An initial amount of 0.45 to 0.60 Gm. intramuscularly is considered the minimal effective dose. Response to each dose should be observed for one and a half to two and a half hours. If conversion to normal rhythm does not occur, the initial dose, or a slightly larger one, should be administered. This preparation is particularly valuable when absorption from the gastrointestinal tract is delayed or unreliable (in the presence of vomiting or shock) and when rapid therapeutic action is desired.

This type of quinidine preparation has been used at the Massachusetts General Hospital since its introduction by Riseman. Besides its use in the situations already mentioned, it has proved of value for seriously ill patients in whom arrhythmias developed after thyroidectomy.

Gefter and Leaman [20] gave 0.5 mg. of ouabain to 33 patients with rapid cardiac arrhythmias of auricular origin. They concluded that it is an effective agent for treating these disorders. No serious toxic effects were encountered, and the incidence of vomiting was low. Like digitalis, the drug was ineffective against simple tachycardias or in the presence of severe complicating infection.

ELECTROCARDIOGRAPHY

In the past few years a schism has arisen among students of electrocardiography, separating them into two well defined schools of thought. The argument centers about the question of validity of Einthoven's equilateral triangle hypothesis. Although the routine work in clinical electrocardiography has not been greatly influenced as yet by the divergence of opinion, the latter may be of importance in determining new directions of investigation. It has already stimulated much lively discussion.

In 1941 Wolferth, Livezey and Wood [21] published the first of their series of articles attacking the Einthoven triangle hypothesis, particularly the assumptions that the body acts as a homogeneous fluid conductor and that the heart functions as an electrical point with regard to each of the three extremities.

In 1942 [22] they reported further observations relating to distribution of potential over the surface of the body. They found that variations in potential along radial lines extending roughly from the heart to the tip of each shoulder did

19. Sturnick, M. I.; Riseman, J. E. F., and Sagall, E. L.: Studies on the Action of Quinidine in Man: Intramuscular Administration of a Soluble Preparation of Quinidine in the Treatment of Acute Cardiac Arrhythmias, J. A. M. A. **121**:917 (March 20) 1943.

20. Gefter, W. I., and Leaman, W. G.: The Use of Ouabain in Rapid Cardiac Arrhythmias, Am. J. M. Sc. **205**:190, 1943.

21. Wolferth, C. C.; Livezey, M. M., and Wood, F. C.: The Relationships of Lead I, Chest Leads from the C-3, C-4, and C-5 Positions, and Certain Leads Made from Each Shoulder Region: The Bearing of These Observations upon the Einthoven Equilateral Triangle Hypothesis and upon the Formation of Lead I, Am. Heart J. **21**:215, 1941.

22. Wolferth, C. C.; Livezey, M. M., and Wood, F. C.: Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms, Am. J. M. Sc. **203**:641, 1942.

not change significantly except for decrement as the distance from the heart increased. These relationships were different from what Einthoven conceived them to be, in the opinion of the authors.

In 1943 the same authors [23] amplified their observations presented in the previous articles and have added further experimental work bearing particularly on potential change below the diaphragm. Their position is aptly summarized in the following sentence:

> If, as our studies seem to indicate, the patterns of potential variation found on limbs are each derived mainly from separate parts of the heart and are subject to modification, depending on electrical and anatomical characteristics of the tissues which form the pathways between the epicardium and the extremities, limb leads do not merit the scientific standing that they have been supposed to possess and there seems to be little reason to continue making them.

The authors believe that there are only three important patterns distributed over the body from the heart as a center, designated as the "C-1" pattern, found on the right side of the chest, the "extra-apical," or "C-5," pattern, found on the left side of the chest, and the "diaphragmatic" pattern, found below the heart and over the abdomen. For routine study they recommend chest leads C-1 to C-6 [24] paired with an indifferent electrode placed at the right scapula, which shows, in their estimation, minimal potential variation. The area below the diaphragm has not been well explored as yet and is suggested as a field for further investigation.

It is suggested that elimination of much of the confusion that now exists in clinical electrocardiography could be effected by dispensing with the limb leads.

The other school of thought, represented by Wilson and his co-workers, uses the Einthoven triangle hypothesis as a working basis for its theories of electrocardiography. While those who belong to this school admit that Einthoven's hypothesis may not be entirely valid, they believe that for most purposes of clinical electrocardiography and for theoretic concept the assumptions are adequate.

Those who support this approach to the subject have used vector analysis in an ingenious fashion to explain the variations in potential found in the electrocardiogram, and in their work the findings in the limb leads are given great importance.

Bayley [25] has written a comprehensive summary of the application of electrocardiographic theory to the interpretation of electrocardiograms. While his approach involves the use of higher mathematics, he has introduced a method of geometric visualization useful to those who are not familiar with advanced mathematics. He states that "the well established laws which define the flow of electric currents in homogeneous volume conductors are applicable to the interpretation of the electrical effects produced by the heart beat with sufficient accuracy to be of great clinical usefulness. The uniformly accurate diagnostic results obtained, particularly in the problem of local myocardial ischemia and infarction, appear to completely justify the adoption by Wilson et al of certain well established physical laws for the interpretation of clinical effects produced by the heart beat."

One of the chief objections held by those who doubt the validity of Einthoven's hypothesis is directed against the assumption that the heart is immersed in a homogeneous electrical medium. The answering argument maintains that this is so for practical purposes, at least, although lung, mediastinal tissue, etc., may not constitute a homogeneous medium in the absolute sense.

Kaufman and Johnston [26] have attempted physical measurements in living tissue in order to answer this question more specifically. The article begins with a technical description of development, properties and use of simple electrode systems employed to measure the specific resistance of living tissue in situ. Measurements were made on muscle, normal inflated lung and liver of anesthetized dogs, and it was found that these tissues have specific resistance in the same order of magnitude. Measurement of the resistance of cardiac muscle during diastole was found to be difficult when the heart was beating rapidly but was approximately one third that of lung, muscle and liver tissue and about the same as that of blood.

In the words of the authors, "these measures establish experimentally the validity of the assumption that the errors in theoretical studies of the form of the electrocardiogram made by considering the tissues which surround the heart

23. Wolferth, C. C.; Livezey, M. M., and Wood, F. C.: Distribution of the Patterns of Ventricular Potential Which Determine the Forms and Significance of Electrocardiograms, Am. J. M. Sc. **205**:469, 1943.

24. Nomenclature and Criteria of Diagnosis of Diseases of the Heart: Criteria Committee of American Heart Association, ed. 4, New York, American Heart Association, 1939.

25. Bayley, R. H.: On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease, Am. Heart J. **26**:769, 1943.

26. Kaufman, W., and Johnston, F. D.: The Electrical Conductivity of the Tissues Near the Heart and Its Bearing on the Distribution of the Cardiac Action Currents, Am. Heart J. **26**:42, 1943.

uniform with respect to their specific resistivity, are of no practical importance."

In 1934 Wilson, Macleod, Barker and Johnston [27] introduced the concept of ventricular gradient as a new method for analysis of the electrocardiogram. The areas of deflections of the QRS complex were used to determine the mean electrical axis of QRS, and the areas of deflections of the T wave were used to determine the mean electrical axis of T, in the same manner that the amplitude of deflection of QRS is ordinarily used to determine the electrical axis of QRS, based on the hypothesis of Einthoven's equilateral triangle. By adding algebraically the area of QRS and the area of T and proceeding in the same fashion it is possible to calculate the direction and magnitude of the manifest area of QRS-T. This quantity is a vector, having both direction and magnitude, to which the name "ventricular gradient" was given by Wilson and his associates. In their opinion the area of QRS-T is a measure of the electrical effects produced by local variations in the excitatory process, while its mean electrical axis gives the direction of the line along which the local variations are greatest.

Ashman, Byer and Bayley [28] offer a clear exposition of the concept of ventricular gradient, using simple examples. They point out that the magnitude and direction of ventricular gradient in conjunction with the QRS vector are an expression of the size and direction of the T wave. A change in the gradient reveals a change in the state of the muscle. Some changes in the T wave, however, such as those in bundle branch block, are directly related to change in QRS.

In a companion article [29] they studied several of the factors, including change in heart rate and posture, which affect Wilson's ventricular gradient and manifest magnitudes of the mean QRS axis. The study implies that changes in the T wave can be evaluated properly only when considered in relation to the magnitude and directions of the mean QRS and QRS-T area. The present chaotic state in electrocardiographic criteria is discussed, and the authors believe that this method of analysis may prove to be a more constant and accurate gage of myocardial change. At the same time, they do not assert that directions of vectors as given necessarily represent their true direction in three-dimensional space. Vector analysis is considered to be of fundamental importance in the solution of electrocardiographic problems.

Further studies of the normal human ventricular gradient were carried out by Ashman, Gardberg and Byer,[30] extending the attempt to set up normal criteria for electrocardiography. Using roentgenograms to define the anatomic axis of the heart, they went on to study the relationship between this entity and the electrical axes (QRS axis and ventricular gradient). A device equipped with a source of light and models of the heart was utilized; the model was projected on a chart. Admittedly much more work must be done before the limits are fixed, but tentative figures have been obtained from this study. The details of these investigations do not lend themselves to a brief review.

Ashman [31] studied the relationship between the magnitudes of the manifest mean areas of the QRS complex, the ventricular gradient and deviations of the RS-T segment. He believes that one type of deviation of the RS-T segment is a normal physiologic phenomenon related to these magnitudes. The second type is related to abatement or reversal in the direction of flow of a current of injury or to intramuscular blocking of a wave of excitation or to a combination of both factors, as in recent myocardial infarction or acute pericarditis.

In the analysis the concept that a diphasic ventricular complex of the electrocardiogram is produced by the summation of two monophasic curves was used with full realization of the limitations of the method. It was shown that the deviations of the RS-T segment observed in human electrocardiograms agreed with the theoretic expectations. It is held that the present terminology for deviation of the RS-T segment is unsatisfactory, because it fails to take into account the two entirely different mechanisms of production of the segment. It is suggested that deviations of the type described in the article be called "repolarization or regression deviations," but those produced by injury or muscle depression and blocking be called "injury

27. Wilson, F. N.; Macleod, A. G.; Barker, P. S., and Johnston, F. D.: The Determination and the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, Am. Heart J. **10**:46, 1934.

28. Ashman, R.; Byer, E., and Bayley, R. H.: The Normal Human Ventricular Gradient: I. Factors Which Affect Its Direction and Its Relation to Mean QRS Axis, with Appendix on Notation, Am. Heart J. **25**: 16, 1943.

29. Ashman, R., and Byer, E.: Normal Human Ventricular Gradient: II. Factors Which Affect Its Manifest Area and Its Relationship to Manifest Area of QRS Complex, Am. Heart J. **25**:36, 1943.

30. Ashman, R.; Gardberg, M., and Byer, E.: The Normal Human Ventricular Gradient: III. The Relation Between the Anatomic and Electrical Axes, Am. Heart J. **26**:473, 1943.

31. Ashman, R.: The Normal Human Ventricular Gradient: IV. The Relationship Between the Magnitudes AQRS and G, and Deviations of the RS-T Segment, Am. Heart J. **26**:495, 1943.

deviations," and that characteristic slight deviations due to the presence of a large ventricular gradient be called "gradient deviations."

Gardberg and Ashman [32] present in graphic fashion, illustrated by models, a way in which vector analysis based on Einthoven's triangle, plus a knowledge of the sequence of activation of parts of the heart, can explain the production of the QRS complex.

They also present explanations of the variations in the QRS complex which should appear when the heart is rotated to different positions within the thorax. In making the analysis they have correlated findings in the experimental animal, known effects of rotation of the heart in man produced by normal procedures or certain pathologic conditions, known effects of bundle branch block or infarction, and information derived from studies of precordial leads.

Viscidi and Geiger [33] criticize the current criteria of normality for the electrocardiogram and report a study of the electrocardiograms of 500 apparently healthy young working adults. One half of the records in the study fell outside the range of normal as defined by the criteria of normality for the American Heart Association.[24] Borderline and abnormal electrocardiograms were then reinvestigated, and only 14 presented either definite or probable abnormalities.

Gubner and Ungerleider [34] suggest specific electrocardiographic criteria for the diagnosis of hypertrophy of the left ventricle. This project was undertaken as part of a study of hypertension, and the material comprised three groups. In the first were 460 applicants for insurance whose electrocardiograms showed deviation of the axis to the left and who had blood pressures below 140 systolic and 90 diastolic, with no record or finding of cardiac impairment. In the second group were 380 applicants with hypertension and deviation of the axis to the left, whose blood pressure was above 140 systolic and 90 diastolic. The third group was made up of 100 subjects with advanced hypertensive heart disease and deviation of the axis to the left in whom it may be assumed that left ventricular hypertrophy was present. Five combinations of R and S waves in the standard limb leads were investigated. The combination of R_1 and S_3 was found to be most efficient. Results of the study are summarized. Hypertrophy of the left ventricle may be considered to be present when deviation of the axis to the left occurs in association with any of the following conditions: (1) increase in amplitude of the QRS complex when the sum of R in lead I and S in lead III is over 2.5 millivolts (hypertrophy is probably present if this sum exceeds 2.2 and is suggested when it exceeds 2); (2) depression of the ST segment in lead I of any perceptible degree, even as slight as 0.5 mm.; (3) flattening of the T wave below 1 mm. in amplitude or further degrees of abnormality of the T wave in lead I.

Increase in amplitude of QRS as described is considered more specific than changes in the ST segment or in the T wave. The authors suggest that the increase in QRS complexes was due to an increase in muscle mass, while the changes in the ST segment and in the T wave resulted from relative ischemia of the subendocardial muscle. That region is particularly vulnerable because of intramyocardial pressure gradient during contraction.

Hurwitz, Langendorf and Katz [35] analyzed the electrocardiograms from 369 cases of myocardial infarction with especial reference to the details of the QRS pattern, in the hope that it might be of use in differential diagnosis of myocardial infarction in the future. The most significant findings were related to the QRS patterns revealed by the limb lead in cases of infarction of the anterior wall. Of special interest was the apparent relative unimportance of the Q_1, T_1 pattern, which was present in only 25 per cent of the cases of anterior infarction. In 32 per cent there was a deep S_2, S_3 pattern, with over one half of these showing a low QRS_1. In the other half of the 32 per cent QRS was normal in size. A low QRS_1 was present in 37 per cent of the cases. On the other hand, in 90 per cent of the 141 cases of infarction of the posterior wall there was a Q_3 or a Q_2, Q_3 pattern.

As far as appraisal of old infarction is concerned, the S_2, S_3 pattern must be differentiated from the picture of left ventricular strain produced by hypertension or valvular heart disease. This is not always possible, but the finding of a low QRS_1 makes the differentiation easy. When QRS_1 is of normal size, the chest leads may be helpful.

Another pattern of interest is that of the inverted QRS_1 with upright QRS_3. This may be differentiated from the picture produced by right ventricular strain with the help of T wave and chest lead patterns.

32. Gardberg, M., and Ashman, R.: The QRS Complex of the Electrocardiogram, Arch. Int. Med. **72**: 210 (Aug.) 1943.

33. Viscidi, P. C., and Geiger, A. J.: Electrocardiographic Observations on 500 Unselected Young Adults at Work, Am. Heart J. **26**:763, 1943.

34. Gubner, R. S., and Ungerleider, H. E.: Electrocardiographic Criteria of Left Ventricular Hypertrophy, Arch. Int. Med. **72**:196 (Aug.) 1943.

35. Hurwitz, M. M.; Langendorf, R., and Katz, L. N.: The Diagnostic QRS Patterns in Myocardial Infarction, Ann. Int. Med. **19**:924, 1943.

Dressler [36] reports an electrocardiographic pattern of value in the diagnosis of myocardial infarction. The significant changes in anterior wall infarction, such as elevation of the ST segment and inversion of the T wave in lead I, are well known. In some instances of infarction of the anterior wall these signs are poorly developed or occur rather late. Instead of sharp inversion there is sometimes but slight flattening of the T wave, which remains upright or becomes isoelectric. In such cases the reciprocal alterations in lead III are often marked. Evidence from his own observations and from reports in the literature indicates that the electrocardiographic pattern in which T_3 is greater than T_1 is in the great majority of cases equivalent to the anterior type of myocardial infarction. This is especially true in the cases of older persons who have a history of angina pectoris.

Other factors may occasionally cause reversal of the normal relationship of T_1 to T_3 (T_1 greater than T_3). A vertical position of the heart in the absence of heart disease, pulmonary emphysema, occasionally rheumatic heart disease, and rarely congenital heart disease, thyrotoxicosis, anemia, vitamin deficiency, uremia and trichinosis may produce the pattern. Dressler reports 45 cases in which a diagnosis of recent or old myocardial infarction could be made on a basis of clinical and laboratory data. In the remaining 25 per cent there was definite evidence of coronary heart disease.

Currens and Barnes [37] studied the autopsy observations in cases of pulmonary embolism with especial reference to the electrocardiograms. Their paper contains an excellent summary of the factors which influence coronary blood flow in pulmonary embolism. An attempt is made to correlate these factors with the electrocardiographic pattern. They discuss coronary reflex effects, fall of arterial pressure, increase in the heart rate, increase in right ventricular pressure produced by obstruction in the pulmonary circuit (which in turn produces a rise in auricular pressure and in pressure in the coronary sinus) and interference with the coronary venous return to the right ventricle through the thebesian veins. The last two effects are of primary importance in altering the flow of blood through the coronary system.

As far as the electrocardiographic picture was concerned, the authors did not attempt to divide their tracings into definite groups. In some of the cases there were no electrocardiograms. Thirty cases in which autopsy was done are reported. There was evidence of acute myocardial infarction in 5 of these. One of the 5 patients had a fresh coronary thrombosis, but the other 4 had none.

In conclusion they state:

> The cause for electrocardiographic changes in pulmonary embolism is considered, and strain on the right ventricle appears to be the determinant factor. The presence of a pulmonocoronary reflex following pulmonary embolism is difficult to prove. It seems likely that compromise in the coronary circulation is best explained by shock and an increase in pressure in the right side of the heart. Decrease in blood flow to the right ventricle from a decrease in arterial pressure gradient, plus an increase in the work of the right ventricle, may account for the occasional association of angina pectoris with pulmonary embolism. Evidence is presented to suggest that asphyxia does not appreciably affect the electrocardiogram in pulmonary embolism.

The importance of using chest leads in the diagnosis of pulmonary embolism is emphasized. Inversion of the T wave in lead CF-2 may be obtained when other leads, including the limb leads, are not diagnostic. Chest leads are of utmost importance to differentiate pulmonary embolism from posterior myocardial infarction.

In this connection it is of interest to refer to the article of Ashman, Byer and Bayley [28] already discussed. They believe that clockwise rotation of the heart around its longitudinal axis as a result of distention of the right side is responsible for the S_1, Q_3 abnormalities. Similar patterns are occasionally seen in normal hearts as a result of such rotation, although of course the changes in the T wave are lacking.

Murnaghan, McGinn and White [38] report further studies on the electrocardiogram in cases of pulmonary embolism. They present 10 new cases of acute cor pulmonale with classic changes: (1) presence of, or tendency toward, deviation of the axis to the right, with a prominent S wave in lead I (ST segment may be slightly depressed in this lead); (2) depressed ST take-off in lead II followed by a rising ST segment and a low upright or diphasic T wave; (3) moderately deep Q wave, slight convexity of the ST segment and an inverted T wave in lead III; (4) a diphasic or more often an inverted T wave in lead IV.

Electrocardiographic changes in an additional series of 92 cases of pulmonary embolism are reviewed. Coexistent heart disease occurred in

36. Dressler, W.: Myocardial Infarction Indicated by an Electrocardiographic Pattern in Which T-1 Is Lower Than T-3, Am. Heart J. **26**:313, 1943.

37. Currens, J., and Barnes, A. R.: The Heart in Pulmonary Embolism, Arch. Int. Med. **71**:325 (March) 1943.

38. Murnaghan, D.; McGinn, S., and White, P. D.: Pulmonary Embolism With and Without Acute Cor Pulmonale, with Especial Reference to the Electrocardiogram, Am. Heart J. **25**:573, 1943.

69. In 29 symptoms of shock predominated. In 63 signs of pulmonary embolism without shock or collapse were present. Electrocardiographic changes considered indicative of acute cor pulmonale were present in 16 cases of the former group and in 17 of the latter. In other words, the electrocardiogram gave indication of some degree of acute cor pulmonale in a little more than one half of the cases when shock predominated, in a little less than one quarter of the group without shock and in about one third of the entire series, including those cases in which the patients had had abnormal electrocardiograms as a result of heart disease.

The authors again emphasize the importance of pulmonary embolism, especially as a complication of acute or chronic illness of a medical nature. Because of the existing confusion in the literature as to the exact place of the electrocardiogram in the diagnosis of pulmonary embolism, the aim of this paper is to clarify the situation by pointing out that the changes may be pathognomonic in the minority of cases, that nondiagnostic changes may occur, as in the case of myocardial ischemia, particularly in the presence of preexisting heart disease, and, lastly, that in many cases of pulmonary embolism one should not expect to find any electrocardiographic changes at all. It is emphasized again that the terms pulmonary embolism and acute cor pulmonale are not synonymous. The latter occurs only in the presence of a high degree of obstruction (thought to be at least 50 per cent) of the pulmonary circuit.

The authors are in agreement with Wood,[39] who pointed out the importance of taking chest leads over the right side of the heart in making the diagnosis of pulmonary embolism. (Since the publication of the paper by Murnaghan and his associates [38] the taking of multiple chest leads in suspected cases of pulmonary embolism has become routine in the cardiac laboratory at the Massachusetts General Hospital.)

Two cases illustrating the clinical course of potassium poisoning in human beings, with characteristic electrocardiographic changes, are reported by Finch and Marchand.[40] In each case there was an acute uremia with oliguria as the underlying cause and therapeutic administration of potassium salts as a complication. Clinical manifestations include recurrent nausea and retching, episodes of bradycardia unaccompanied by symptoms of cardiac failure or changes in blood pressure and a sudden ascending flaccid quadriplegia without paralysis of the trunk or disturbances of speech or mental function.

The electrocardiographic changes include elevation of T waves, absence of P waves, intraventricular block and terminal irregularity of the rhythm. Arrest of the heart in diastole prior to cessation of respiration was observed. These findings extended the observations of Winkler, Hoff and Smith,[41] who several years ago defined the electrocardiographic diagnosis of potassium poisoning in man.

Keith, King and Osterberg,[42] in discussing potassium levels in severe renal insufficiency, include an electrocardiogram which shows all of the changes just described.

Brown, Currens and Marchand [43] report 3 interesting cases of muscular paralysis occurring in association with chronic nephritis and having the characteristics of the disability seen in familial periodic paralysis. In these cases it was considered that the paralysis resulted from excessive loss of potassium by the body. Electrocardiographic changes were similar to those observed in periodic paralysis and in depletion of serum potassium from other causes. In all 3 instances the T waves in the electrocardiogram were low and returned to normal with subsidence of the paralysis. Depressed ST segments were also observed, and in one case there was a disturbance of auriculoventricular conduction with Wenckebach periods.

Mazer and Reisinger [44] contribute a study pertaining to changes in the Q wave in the electrocardiogram. The electrocardiographic records of 102 hospitalized patients showing a Q wave in lead III were analyzed. In every instance the Q wave in lead III was at least 25 per cent of the highest R wave in the limb leads. In this group of patients 18.6 per cent had no heart disease. More severe criteria were then applied, and it was discovered that fewer normal persons satisfied them. Among the persons whose records showed Q_3 equal to 100 per cent or more of the highest R wave, only 42 per cent of the patients

39. Wood, P.: Pulmonary Embolism: Diagnosis by Chest Lead Electrocardiography, Brit. Heart J. **3**:21, 1941.

40. Finch, C. A., and Marchand, J. F.: Cardiac Arrest by the Action of Potassium, Am. J. M. Sc. **206**:507, 1943.

41. Winkler, A. W.; Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injections of Potassium Chloride, Am. J. Physiol. **124**:478, 1938.

42. Keith, N. M.; King, H. E., and Osterberg, A. E.: Serum Concentration and Renal Clearance of Potassium in Severe Renal Insufficiency in Man, Arch. Int. Med. **71**:675 (May) 1943.

43. Brown, M. R.; Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, J. A. M. A. **124**:545 (Feb. 26) 1944.

44. Mazer, M., and Reisinger, J. A.: Criteria for Differentiating Deep Q-3 Electrocardiograms from Normal and Cardiac Subjects, Am. J. M. Sc. **206**:48, 1943.

with organic heart disease satisfied the criteria, but it is of interest that 16 per cent of the normal subjects were included. Although increasing the severity of the criteria resulted in elimination of more normal subjects, some were still included. Thus it does not appear that such criteria are of great value in assessing the condition in an individual case. It also seems possible that some of the waves designated Q were actually QS deflections.

The effects of digitalis on the electrocardiogram were studied by Dearing, Barnes and Essex [45] as part of an investigation to determine the toxic effect of various preparations of digitalis on the myocardium.[46] With therapeutic doses the changes were minor, consisting of decrease or increase of the height of the T wave in one or more leads or a change in the direction of T_3. None of the abnormalities described could be considered a reliable index to the presence of a calculated amount of therapeutic digitalis. It was also concluded that the change in heart rate was an unreliable guide.

With toxic doses abnormalities in addition to those just mentioned were seen. These consisted of depression of the RS-T segment in one or more leads, a plus-minus change in the RS-T segment, elevation of the RS-T segment (plateau type) in one or more leads, cove-plane negative T_2 and T_3 with positive T_1, and positive T_2 and T_3. The last four anomalies described were associated with definite microscopic myocardial lesions. However, two animals with myocardial lesions failed to show significant changes in their daily electrocardiograms.

Thompson [47] reports a study of the electrocardiographic changes in 25 patients with the hyperventilation syndrome. Abnormalities consisted chiefly of late inversion of the T wave or of depression of the ST segment with marked lowering of the T wave. Any or all leads may be involved. In only 1 case was there a change in the QRS complex, and this was observed in lead 4-F. Neither the degree of alkaline shift nor the extent of lowering of the carbon dioxide–combining power appeared to be the sole factor in determining the kind or magnitude of changes in ST and T, nor did these changes necessarily depend on changes in the heart rate.

Since severe precordial pain may be included in the syndrome, recognition of these marked electrocardiographic abnormalities is important, lest they be attributed to infarction of the heart.

Ever since the syndrome of bundle branch block associated with short PR interval was described by Wolff, Parkinson and White,[48] a number of theories have been advanced to explain the findings. One of the most popular has assumed the existence of an accessory bundle of conducting tissue (Bundle of Kent) connecting the auricle with the ventricular cavity. Wood, Wolferth and Geckeler [49] present etiologic proof of an accessory muscular connection between auricles and ventricles found at autopsy in a patient with the characteristic Wolff, Parkinson and White syndrome.

Serial histologic sections of a portion of the auriculoventricular groove showed three muscular connections at the right lateral border of the heart between the right auricle and the right ventricle. It was concluded that this furnished further support for the hypothesis of an accessory pathway of auriculoventricular conduction as an explanation for the anomaly. Adequate control studies are still lacking, however.

Fox, Travell and Molofsky [50] report a case in which prolongation of the QRS interval was produced repeatedly by digitalis in a patient whose electrocardiograms taken during the digitalis effect showed a short PR interval with a QRS of characteristic configuration. The QRS interval measured only 0.09 second in the absence of digitalis. The prolongation was abolished by atropine. It is stated that the results of this study are in harmony with the hypothesis favoring an aberrant conduction mechanism. The widening of QRS was thought to be the result of depression of the auriculoventricular node, producing increased activity of the aberrant ventricular conduction tissue, rather than of an action of digitalis on intraventricular conduction.

45. Dearing, W. H.; Barnes, A. R., and Essex, H. E.: Experiments with Calculated Therapeutic and Toxic Doses of Digitalis: II. Effects on Electrocardiogram, Am. Heart J. **25**:665, 1943.

46. Dearing, W. H.; Barnes, A. R., and Essex, H. E.: Experiments with Calculated Therapeutic and Toxic Doses of Digitalis: Effects on Myocardial Cellular Structure, Am. Heart J. **25**:648, 1943.

47. Thompson, W. P.: The Electrocardiogram in the Hyperventilation Syndrome, Am. Heart J. **25**:372, 1943.

48. Wolff, L.; Parkinson, J., and White, P. D.: Bundle-Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, Am. Heart J. **5**:685, 1930.

49. Wood, F. C.; Wolferth, C. C., and Geckeler, G. D.: Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, Am. Heart J. **25**:454, 1943.

50. Fox, T. T.; Travell, J., and Molofsky, L.: Action of Digitalis on Conduction in the Syndrome of Short PR Interval and Prolonged QRS Complex, Arch. Int. Med. **71**:206 (Feb.) 1943.

Phang and White [51] report studies on the QT interval in cardiac enlargement. A significant relative prolongation of the QT interval was found in the majority of cases of cardiac enlargement without concomitant congestive failure. It was found that congestive heart failure produced a still greater prolongation. The QT interval showed a relative shortening after recovery from failure, while the patients were still under the influence of digitalis. It was concluded that cardiac enlargement was one of the factors responsible for prolongation of the QT interval, because of the longer pathways of impulse conduction and the greater bulk of contracting muscle. Thus digitalis may affect the duration of systole chiefly by increasing the heart tone, which in turn brings about a decrease in its size.

ROENTGENOLOGY

Meneses Hoyos and Quesada [52] studied the cardiovascular roentgen silhouette in normal cadavers by injecting a 50 per cent solution of sodium iodide into large vessels and heart chambers. Roentgenograms were then taken in the posteroanterior, right anterior oblique and left anterior oblique positions. Of special interest were their findings concerning the composition of the left side of the cardiac outline, in view of the past controversy over that point. They concluded that the left side of the outline is made up from above downward of (1) a straight segment corresponding to the left carotid and left subclavian arteries, (2) a middle arch composed of the left division of the pulmonary artery in its upper portion, the main pulmonary artery in its middle portion and the left auricle in its lower portion and (3) the main segment, made up of the left ventricle.

Sussman, Grishman and Steinberg [53] used intravenous injection of 70 per cent diodrast to study the problem of right-sided enlargement of the heart. Serial roentgenograms were taken to determine the outline of the great vessels and heart chambers as visualized by the diodrast. It was their purpose to reexamine the older criteria for right ventricular enlargement, set forth by Kirch and summarized by Schwedel.[54] In their analysis of cases of emphysema several persons with normal cardiac configurations by the usual method showed marked right ventricular dilatation when the right ventricle was outlined with the contrast medium. It was shown that the intraventricular septum bulged to the left and the right ventricular apex was widened, neither of which patterns is evident in an ordinary roentgenogram. It was of interest that a bulging right anterior curve in the left oblique position, supposedly a sign of right ventricular enlargement by the old criteria, was encountered only exceptionally.

Angiocardiography in cases of mitral stenosis revealed that the prominent middle left segment seen in the posteroanterior view consisted of the dilated left auricular appendage or atrium in most cases. Thus prominence of the middle segment is not a direct indication of right ventricular enlargement. They found also that the pulmonary artery is not significantly dilated in mitral stenosis but that enlargement of the left auricle may produce elevation of the pulmonary valve and elongation with anterior and cephalad displacement of the pulmonary artery.

In cor pulmonale great dilatation and tortuosity of the pulmonary artery produced a bulge of the middle left cardiac segment. In contrast to the statement found in the old criteria that the outflow tract of the right ventricle contributes to this prominence, it was shown that the pulmonary conus actually did not contribute to the left cardiac contour, although dilatation of the right ventricle produced elevation of the pulmonary artery and contributed to its tortuosity. The authors pointed out that enlargement of the heart to the right with bulging of the right anterior contour in the absence of left ventricular enlargement indicates dilatation of the right auricle in addition to right ventricular involvement. This is said to be of grave prognostic significance because of its usual occurrence in the presence of heart failure.

CONGENITAL HEART DISEASE

Keys and Shapiro,[55] faced with the problem of setting up criteria for surgical intervention in cases of patent ductus arteriosus, were stimulated to further investigation into the history of the untreated disorder. It is a common clinical impression that the congenital anomaly of patency of the ductus arteriosus is a comparatively innocuous lesion. In order to determine

51. Phang, S. H., and White, P. D.: The Duration of Ventricular Systole as Measured by the Q-T Interval of the Electrocardiogram, with Especial Reference to Cardiac Enlargement With and Without Congestive Failure, Am. Heart J. **26**:108, 1943.

52. Meneses Hoyos, J., and Quesada, J. J.: Normal Cardiovascular Roentgen Silhouette, Arch. Int. Med **71**:666 (May) 1943.

53. Sussman, M. L.; Grishman, A., and Steinberg, M. F.: The Roentgenologic Diagnosis of Right-Sided Enlargement of the Heart, New England J. Med. **228**: 777, 1943.

54. Nomenclature and Criteria for Diagnosis of Diseases of the Heart: Criteria Committee of the New York Heart Association, ed. 4, New York, New York Tuberculosis and Health Association, 1939.

55. Keys, A., and Shapiro, M. J.: Patency of Ductus Arteriosus in Adults, Am. Heart J. **25**:158, 1943

what happens to the older persons with this disability, they analyzed 67 autopsy records from the world literature and from 4 cases of their own. In over 40 per cent of the cases subacute bacterial endarteritis was the cause of death. Twenty-eight per cent of the patients died of congestive failure, and in 2 cases rupture of a pulmonary aneurysm was the final event. After the age of 17 years patency of the ductus arteriosus was associated with an average reduction of life expectancy of about twenty-five years. From this extensive survey it was concluded that "the great majority of patients with this defect suffer no serious disability or restriction of activity during most of their life, but their life expectation is greatly shortened by continued presence of the defect."

In another report the same authors [56] investigated the results of 140 operations submitted by surgeons experienced in the technic. It was shown that the over-all mortality was less than 10 per cent and that in the presence of subacute bacterial endarteritis ligation offers an even chance of survival. It is their opinion that the majority of patients should have ligation performed after careful clinical study, although the danger of development of subacute bacterial endocarditis after successful ligation cannot be properly evaluated as yet. The question of operation in cases of subacute bacterial endarteritis is discussed in another section.

Another factor to be considered when one is contemplating an operation on an older patient is the greater technical difficulty frequently encountered as a result of shortening of the ductus. And in any case there still remains a definite operative risk that must be considered in the case of a person who at the time of operation may be in good health.

Araya and White [57] were interested in the possibility of a relationship between prematurity of birth and congenital cardiovascular defects. Autopsy protocols of prematurely born babies were examined, and only 3 cases (2.2 per cent) of congenital malformation were encountered in a series of 139 autopsies. The incidence of congenital heart disease in relation to prematurity of birth was also investigated. Of 148 patients whose birth weights were normal, 17 weighed less than 2,500 Gm. at birth (11.4 per cent). In 172 cases in which the duration of pregnancy was ascertained, 17 infants were born prematurely (9.8 per cent). Thus in cases of congenital heart disease the incidence of prematurity of birth was twice that in deliveries of infants with normal hearts. However, only 1 patient out of 19 with patency of the ductus arteriosus, which is in reality a postnatal development, weighed less than 2,500 Gm. at birth.

56. Shapiro, M. J., and Keys, A.: The Prognosis of Untreated Patent Ductus Arteriosus and the Results of Surgical Intervention, Am. J. M. Sc. **206**:174, 1943.

57. Araya, E., and White, P. D.: The Relationship of Congenital Heart Disease to Premature Birth, Am. Heart J. **25**:449, 1943.

BACTERIAL ENDOCARDITIS

Although there are reports of cures in isolated cases of subacute bacterial endocarditis following the use of sulfonamide compounds, with or without adjuvants, this method of therapy on the whole continues to be disappointing.

Lichtman [58] submits a comprehensive report on a total of 704 cases, including 98 of his own and 606 from the literature. The average incidence of recovery was 5.5 per cent. The combination of fever treatment with chemotherapy appeared to offer the best possibilities.

There has been great interest in the possibility that penicillin might prove effective in the treatment of this largely fatal disorder. The commission appointed by the National Research Council on penicillin [59] has submitted a preliminary unfavorable report. Further studies with larger doses are in progress and the results are much more promising, but the duration of the follow-up is far too short for any adequate appraisal.

Loewe, Rosenblatt, Greene and Russell [60] report on a series of 7 consecutive patients apparently treated successfully with a combination of penicillin and heparin. Six patients had underlying chronic rheumatic valvular disease, while the other had a congenital cardiac lesion. Streptococcus viridans was the infecting organism in 5, hemolytic strepticocci in 1 and pneumococci in 1. The daily dose of penicillin varied from 40,000 to 200,000 Florey units. The dose of heparin averaged about 200 mg. daily when given intravenously and 300 mg. every second day when given subcutaneously. The results indicated successful sterilization of the blood and relief of clinical manifestations, although admittedly further observations will be required before these patients can be pronounced cured. In no case was the total elapsed time since the beginning of treatment more than one year on the date of publication.

58. Lichtman, S. S.: Treatment of Subacute Bacterial Endocarditis: Current Results, Ann. Int. Med. **19**:787, 1943.

59. Keefer, C. S.; Blake, F. G.; Marshall, E. K.; Lockwood, J. S., and Wood, W. B.: Penicillin in the Treatment of Infections, J. A. M. A. **122**:1217 (Aug. 28) 1943.

60. Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, J. A. M. A. **124**: 144 (Jan. 15) 1944.

The efficacy of ligation of the patent ductus arteriosus in the treatment of subacute bacterial endarteritis complicating that condition is discussed by Touroff.[61] He reports on a series of 11 patients subjected to operation after the complication of subacute bacterial endarteritis had set in. Two died from complications of operation, and 6 of the 9 survivors recovered without the benefit of chemotherapy. The 3 remaining patients did not recover, in spite of chemotherapy. There was no evidence of preoperative spread of the infection to the cardiac valves or the aorta in any of the 6 who recovered. On the other hand, there was evidence of valvular involvement preoperatively in 3 of those who did not recover. The third was assumed to have had vegetations at the aortic end of the ductus. These observations suggest that operation should be undertaken as soon as a diagnosis of subacute bacterial endarteritis is established. In the present state of development of medical therapy, it may be dangerous to submit the patient to a therapeutic trial of drugs before surgical intervention is attempted.

RHEUMATIC HEART DISEASE

Koletsky [62] presents an interesting observation related to the problem of bacterial infection of a bicuspid aortic valve. Congenital heart disease has generally been assigned an important role among the underlying factors concerned with the development of bacterial endocarditis. Bicuspid aortic valve is one of the congenital lesions, along with patent ductus arteriosus and patent interventricular septal defect, which has generally been considered important in this connection. In Koletsky's study 50 adult hearts with bicuspid aortic valve were carefully examined at autopsy; 8 of these showed superimposed bacterial endocarditis. In every specimen of the latter group superimposed bacterial endocarditis involved the bicuspid valves. However, gross changes indicative of rheumatic valvular disease were present on the aortic valves in each instance, including 1 in which a congenital bicuspid lesion was complicated by the rheumatic changes. Of the total of 50 cases of this congenital abnormality, in 40 the disease was acquired and in 10 it was congenital. He concluded that most bicuspid aortic valves in adults are acquired lesions, produced by rheumatic fever. It is the latter, in his opinion, rather than the bicuspid state, which is of importance in the development of bacterial endocarditis. The article contains a good summary of contributions in the literature bearing on the question of bicuspid valves. Criteria for differentiation are given.

Further evidence is accumulating to show that recrudescence of rheumatic fever may be prevented by the use of sulfonamide drugs. This was well demonstrated in the work of Kuttner and Reyersbach,[63] reviewed in last year's summary of articles on diseases of the heart.[13]

Messelhoff and Robbins [64] used sulfanilamide in daily doses of 20 grains (1.2 Gm.) given to 25 ambulatory rheumatic children. Thirty rheumatic children were used as controls. The patients in the group receiving treatment were observed over two periods of eight months, extending from September to May, and there were 1 recrudescence of rheumatic fever and 2 deaths, 1 from congestive heart failure and 1 from subacute bacterial endocarditis. In the nontreated group 1 patient died from congestive failure and there was one recrudescence of rheumatic fever. From this short series it was not possible to conclude that sulfonamide drugs are especially effective in preventing recurrence of rheumatic fever.

However, the results presented in another report made in 1942 by Hansen, Platou and Dwan [65] are in agreement with the findings of Kuttner and Reyersbach. The consensus among workers in the field is that the method offers definite promise.

Coburn [66] reports his experiences with salicylate therapy in rheumatic fever. It is his belief that the inflammatory reactions of the disease can be suppressed by salicylate therapy, with resultant inhibition of pathologic change in valves and myocardium. The factor of rheumatic infection is apparently not modified by therapy. A simple method for the determination of the salicyl radical is described, providing more effective therapeutic control through measurement of blood levels of the drug. The intravenous use of sodium salicylate is advocated in the first stages

61. Touroff, A. S. W.: The Results of Surgical Treatment of Patency of the Ductus Arteriosus Complicated by Subacute Bacterial Endarteritis, Am. Heart J. **25**:187, 1943.

62. Koletsky, S.: Bicuspid Aortic Valves and Bacterial Endocarditis, Am. Heart J. **26**:343, 1943.

63. Kuttner, A. G., and Reyersbach, G.: The Prevention of Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, J. Clin. Investigation **22**:77, 1943.

64. Messelhoff, C. R., and Robbins, M. H.: The Prophylactic Use of Sulfanilamide in Children with Rheumatic Heart Disease, J. Lab. & Clin. Med. **28**: 1323, 1943.

65. Hansen, A. E.; Platou, R. V., and Dwan, P. F.: Prolonged Use of a Sulfonamide Compound in Prevention of Rheumatic Recrudescence in Children: An Evaluation Based on a Four Year Study on Sixty-Four Children, Am. J. Dis. Child. **64**:963 (Dec.) 1942.

66. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: A Rational Technique, Bull. Johns Hopkins Hosp. **73**:435, 1943.

of active rheumatic infection. Further evaluation is needed, and the possibility of severe toxic reactions must be kept in mind. The drug may have a profound effect on body metabolism in larger doses.[67]

HYPERTENSION

Investigation of the problem of hypertension by the experimental approach, with especial reference to a humoral mechanism of renal origin, continues to need follow-up. It is impossible to attempt a comprehensive review of this complex subject in a brief article.

Page and co-workers [68] have published a progress report of the experimental treatment of hypertension with renal extracts, in which the concept that renal ischemia is not essential to the production of hypertension is reiterated. Reduction of renal pulse pressure is thought to be a more essential mechanism. Improvement in the quality of renal extracts has been achieved, in that reactions have been reduced, but as yet the yield of active substance is low. An in vitro method for assay of renal extract has been developed, which depends on the ability of the extract to destroy angiotonin. However, it has also been observed that with reduction in severity of reaction antipressor activity has also been lessened. The author still supports the concept of a humoral mechanism in which kidney substance, renin, interacts with renin activator to produce an effective vasoconstrictor agent, angiotonin.

Further studies have been carried out to show that this vasoconstrictor substance exhibits properties similar to those seen in hypertension. This is reported in detail in an article by Taylor and Page,[69] in whose experiments the reaction of the cardiovascular system in human beings was measured by the ballistocardiograph. Angiotonin administered to patients with normal cardiovascular systems reduced the stroke volume and cardiac output as measured by that instrument. On the other hand, when the antipressor angiotonin-destroying renal extract was given to hypertensive patients, the cardiac output increased and the contour of the curve bore a closer resemblance to the normal. These findings differed from those obtained with other pressor substances (methyl guanidine or tyramine).

In the progress article already mentioned, Page and his associates [68] state that clinical results obtained with the antipressor renal extract in 37 patients continue to be encouraging. Twenty-four of these had malignant hypertension, and 9 died. Reversal of changes in the eyegrounds with improvement of vision, reversal of the abnormal electrocardiographic picture to a more normal pattern and decrease in diastolic blood pressure with increase in cardiac output were the most striking changes in the group with malignant hypertension.

Plentl and Page [70] studied the nature of renin and angiotonin by means of a kinetic analysis of the renin-angiotonin pressor system. For a more complete account of the work on the subject of the mechanism of the production of hypertension done during the past year, reference should be made to various articles.[71]

Lisa, Eckstein and Solomon [72] describe the condition of the main renal arteries in 100 consecutive patients coming to autopsy at the City Hospital, Welfare Island, New York. Studies were carried out on tissues in the fresh state to eliminate the error produced by shrinkage with fixation. There were 56 hypertensive subjects and 44 without hypertension. The differences in caliber between the sclerotic vessels in the two groups were insignificant, and the authors concluded that arteriolar sclerosis is a better index of blood pressure than the caliber of the

67. Barnett, H. L.; Powers, J. R.; Benward, J. H., and Hartmann, A. F.: Salicylate Intoxication in Infants and Children, J. Pediat. **21**:214, 1942.

68. Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Kempf, G. F.; Corcoran, A. C., and Taylor, R. D.: Progress Report of Investigations Concerned with the Experimental Treatment of Hypertension with Kidney Extracts, Ann. Int. Med. **18**:29, 1943.

69. Taylor, R. D., and Page, I. H.: The Effect of Antipressor Kidney Extract, Angiotonin (etc.) on Cardiac Output as Measured by the Ballistocardiograph in Hypertensive and Normal Persons, Am. J. M. Sc. **205**:66, 1943.

70. Plentl, A. A., and Page, I. H.: A Kinetic Analysis of the Renin-Angiotonin Pressor System and the Standardization of the Enzymes Renin and Angiotonase, J. Exper. Med. **78**:367, 1943.

71. (*a*) Leiter, L., and Eichelberger, L.: Duration of Pressor Effect of Large Doses of Renin (Kidney Extract) in Conscious Normal and Renally Abnormal Dogs: Observations on Anesthetized and Uremic Dogs and Anaphylactic and Pathological Effects of Pig Renin, J. Clin. Investigation **22**:11, 1943. (*b*) Plentl, A. A., and Page, I. H.: Enzymatic Nature of Angiotonin Formation from Renin (Kidney Extract) and Renin Activator, J. Biol. Chem. **147**:135, 1943. (*c*) Page, I. H.: Newer Concepts of Mechanism of Arterial Hypertension, J. Omaha Mid-West Clin. Soc. **4**:23, 1943. (*d*) White, B. V.; Durkee, R. E., and Mirabile, C.: Renal Hypertension: Review of the Status, Including Report of a Case of Hypertension Relieved After Nephrectomy, New England J. Med. **228**:277, 1943. (*e*) Goldblatt, H.; Katz, Y. J.; Lewis, H. A., and Richardson, E.: Bioassay of Renin (Kidney Extract), J. Exper. Med. **77**:309, 1943. (*f*) Grollman, A.; Harrison, T. R., and Williams, J. R.: Mechanism of Experimental Renal Hypertension in the Rat: Relative Significance of Pressor and Antipressor Factors, Am. J. Physiol. **139**: 293, 1943.

72. Lisa, J. R.; Eckstein, D., and Solomon, C.: Relationship Between Arteriosclerosis of Renal Artery and Hypertension: Analysis of One Hundred Necropsies, Am. J. M. Sc. **205**:701, 1943.

main renal arteries. They believe that gross reduction of blood flow resulting from arteriosclerosis of the main renal arteries is of less importance than lowering of pulse pressure within the kidney.

One of the circumstances which has hampered the investigation of hypertension in human beings is the fact that most of the autopsy material has been obtained from patients with hypertension of long standing. Opportunities to study the histologic changes in the kidney in early hypertension have been few. The pioneer investigations of Castleman and Smithwick [73] in this direction are of much importance. In the course of bilateral extensive splanchnic denervation (sympathectomy) done on 100 hypertensive patients, renal biopsies were made. This group included persons with all degrees of the hypertensive state, with changes in the eyegrounds varying from arteriolar narrowing or constriction without nicking (grade I) to edema of the optic disks with measurable elevation, usually accompanied by hemorrhage, exudate and other abnormalities (grade IV). Fourteen per cent of the subjects showed changes of grade IV. The average findings in the series were: blood pressure, 210 systolic and 130 diastolic; age, 39; duration, six years. The renal function as measured by the phenolsulfonphthalein test was normal in 60 per cent of the subjects. Insignificant or no vascular renal disease was evident in 28 per cent of the biopsies, and only mild changes occurred in an additional 25 per cent.

It was concluded that "the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing hypertension, and that in many of these and probably others the hypertensive state antedated the renal vascular lesion, which, once established, probably aggravated the hypertension. Furthermore, these observations are not in keeping with the concept that renal ischemia due to preexisting renal vascular disease is the cause of essential hypertension in man."

Talbott and Castleman and co-workers [74] correlated the observations in renal biopsies with results of studies of renal clearance done on 20 patients with essential hypertension. It was discovered that the glomerular filtration rate and the renal blood flow were most significantly reduced in the patients who showed the most advanced changes of renal vascular disease by biopsy. They found the filtration fraction normal in 7 of 8 patients in the group showing late or no pathologic change in the kidneys. The authors believed that the observations indicated that constriction of the efferent glomerular arterioles was not present in the early stages of renal vascular disease. Lumbodorsal splanchnicetomy had little effect on renal clearance when measured in the horizontal position.

An important approach to the present day treatment of hypertension is surgical splanchnic denervation. The extensive operation of dorsolumbar sympathectomy developed by Smithwick and previously reported [75] has been in continued use by this author at the Massachusetts General Hospital in the treatment of hypertension. The details of this work are as yet unpublished, but the clinical results in selected cases are impressive, with regard both to lowering of the blood pressure, systolic and diastolic, and to subjective improvement.

An interesting report was made by Friedman and Kasanin,[76] who described the occurrence of hypertension in one of identical twins with definite evidence of disease of the coronary arteries shown by the electrocardiogram and by clinical findings. The other twin had a normal blood pressure and electrocardiogram. Both had a diminished renal blood flow as compared with the average value of 1,280 cc. per minute. In the patient with hypertension the flow as calculated was 606 cc. per minute, while in the normal brother the figure was 725 cc. per minute. Difference in personality was striking. The descriptive terms dynamic, aggressive, energetic, active and successful were applied to the twin with high blood pressure, while the normal brother was more alert mentally and stronger physically but lacking in "drive." No conclusions are drawn, but it is suggested that a possible cause of the hypertension may lie in the divergent personality trends, especially in view of the similarity in heredity and early environment. Because of the fact that the renal blood flow was somewhat reduced in the so-called normal twin, it will be of interest to see if he also eventually has hypertension.

73. Castleman, B., and Smithwick, R. H.: The Relation of Vascular Disease to the Hypertensive State, Based on a Study of Renal Biopsies from One Hundred Hypertensive Patients, J. A. M. A. **121**:1256 (April 17) 1943.

74. Talbott, J. H.; Castleman, B.; Smithwick, R. H.; Melville, R. S., and Pecora, L. J.: Renal Biopsy Studies Correlated with Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy, J. Clin. Investigation **22**:387, 1943.

75. Smithwick, R. H.: A Technic for Splanchnic Resection for Hypertension, Surgery **7**:1, 1940.

76. Friedman, M., and Kasanin, J. S.: Hypertension in Only One of Identical Twins, Arch. Int. Med. **72**: 767 (Dec.) 1943.

CORONARY HEART DISEASE

Askey,[77] in reviewing the syndrome of painful disability of the shoulder and hand following coronary occlusion, suggests that some of the changes in the palmar aponeurosis may be related to myocardial infarction. Moreover, Kehl[78] reports 6 cases of Dupuytren's contracture following coronary occlusion within a period of eleven months. In no case was there any evident relationship to trauma or any change before the thrombosis occurred. Pain, stiffness, swelling, repeated discoloration, numbness, tingling and coldness of the hands were encountered with the contracture. Four of the patients also had pain in the shoulder. Johnson[79] reports clinical observations in 39 cases in which disabling changes in the hands resembling sclerodactylia followed myocardial infarction. In a period varying from three to sixteen weeks after infarction occurred, pain and stiffness of the fingers appeared, with nonpitting swelling of the hands. Evidence of circulatory change was seen in the form of coldness and change in color, which varied from erythema to cyanosis. At a later date thickening of the skin, atrophy of the soft tissue and in some cases palmar contracture occurred. The changes described bore a close resemblance to the sclerodactylia of scleroderma and Raynaud's disease. The "anginal syndrome" was present in every case. Pain in the shoulder occurred in 34 patients and bore some relation to the site of radiation of anginal pain. The changes in the hand were bilateral. Arthritis did not appear to be an important factor in the genesis of this syndrome. Although 10 patients had a brief "rheumatic" history, none had had previous rheumatoid arthritis, and 4 had had hypertrophic arthritis. It is emphasized that the changes described do not progress to gangrene and trophic ulceration of the fingers, in spite of their resemblance to the sclerodactylia of Raynaud's disease. The possible etiologic relationships are discussed.

Starr and Wood[80] used the ballistocardiogram to study the circulation in patients with coronary artery disease, including acute myocardial infarction and chronic angina pectoris. One hundred and six observations were made on 55 patients having those diseases. Measurements of the circulation with the ballistocardiograph were either normal or below normal in the acute period after infarction. In the first instance the circulation tended to diminish and reached a minimum between the third and the fifth week, with later recovery. In the great majority of cases of chronic coronary disease with angina of effort the circulation was abnormal. Abnormalities of form in the tracing were frequently encountered in association with coronary heart disease. Limitations of this method are manifested with regard to the diagnosis of anatomic lesions. The measurements gave objective aid in making the diagnosis but should be regarded as of the same order of significance as measurements of blood pressure, etc.

Master, Jaffe, Dack and Silver[81] followed the course of the blood pressure in 538 cases of coronary occlusion over an average period of three and a half to four years (range, one to seven years). In every case the blood pressure fell to some extent, although the occurrence of a transitory rise at the beginning was observed in a few. The lowest pressure was usually reached between the twelfth and the twentieth day. In comparing the data for the hypertensive and the nonhypertensive subjects it was observed that the blood pressure trend was similar, although among the nonhypertensive patients who died a rapid fall was more common. Two thirds of the hypertensive patients regained a hypertensive level, but one half of this group showed a delayed rise over a period of one to two years. It was concluded that the height of the blood pressure after the attack did not influence the future course of the patient significantly with respect to subsequent angina pectoris, heart failure, coronary occlusion or death.

White, Bland and Miskall[82] have collected important data relating to the prognosis of angina pectoris. It is their contention that the only accurate basis for prognosis in that disease is a long time follow-up of a large group of patients through the entire course of the disease. Their report consists of a further follow-up of 497 patients with angina pectoris first observed in

77. Askey, J. M.: The Syndrome of Painful Disability of Shoulder and Hand Complicating Coronary Occlusion, Am. Heart J. **20**:1, 1941.

78. Kehl, K. C.: Dupuytren's Contracture as a Sequel to Coronary Artery Disease and Myocardial Infarction, Ann. Int. Med. **19**:213, 1943.

79. Johnson, A. C.: Disabling Changes in the Hands Resembling Sclerodactylia Following Myocardial Infarction, Ann. Int. Med. **19**:433, 1943.

80. Starr, I., and Wood, F. C.: Studies with Ballistocardiograph in Acute Cardiac Infarction and Chronic Angina Pectoris, Am. Heart J. **25**:81, 1943.

81. Master, A. M.; Jaffe, H. L.; Dack, S., and Silver, N.: The Course of the Blood Pressure Before, During, and After Coronary Occlusion, Am. Heart J. **26**:92, 1943.

82. White, P. D.; Bland, E. F., and Miskall, E. W.: The Prognosis of Angina Pectoris: A Long Time Follow-Up of 497 Cases, Including a Note on 75 Additional Cases of Angina Pectoris Decubitus, J. A. M. A. **123**:801 (Nov. 27) 1943.

the years from 1920 to 1930.[83] Of this number 445 patients were dead and 52 were living. The average duration of life of the dead patients was seven and nine-tenths years after the onset of symptoms, while for the 52 living patients the average duration of the disease was eighteen and four-tenths years. The average for both living and dead patients is nine years to date, which is considerably higher than the "classic and often quoted figure of five years." The factors of hypertension, myocardial infarction, cardiac enlargement, abnormal heart sounds, congestive failure and abnormal electrocardiogram occurred much more frequently in the group of patients who died within three years than in the 52 patients still living. The authors also inquired into the prognostic significance of angina pectoris decubitus, which was present in 20 per cent of the total number.

Much has been written in recent years concerning the mechanism of production of coronary occlusion, and it has been held that bleeding from vascular channels of the intima of a vessel may cause arterial occlusion, either directly by producing local hematoma or indirectly by thrombus formation near the site of the hemorrhage.

English and Willius[84] investigated this question by means of autopsy studies. One hundred and thirty-five selected hearts were examined, 40 per cent of which showed intimal hemorrhage. There was acute occlusion of the coronary artery in 20 specimens. Wherever hemorrhage was encountered in the intima of a coronary artery, coexistent degenerative changes were found. It was concluded that the intimal degenerative changes represented the primary factor in the pathologic condition, while the hemorrhage was secondary.

Steiner and Domanski[85] studied the serum cholesterol level in 15 patients with coronary heart disease and in 15 controls of the same age. They made repeated observations over periods up to two years. The level in the patients with coronary arteriosclerosis was found signficantly higher than that in the normal subjects, with wide fluctuations characterizing the former group and fairly constant levels occurring in the latter group.

Engelberg and Newman[86] have reported 6 instances of disease of the coronary arteries in young adults with xanthomatosis. In each case three characteristic features were present. The cutaneous lesions consisted of single or multiple firm subcutaneous nodules of variable size, found mostly on the extensor surfaces of the extremities. In every case the diagnosis of coronary insufficiency was made, and all the patients showed hypercholesteremia. The results of treatment with low cholesterol diet were inconclusive. Only 3 of the patients followed the diet faithfully, and in only 1 was there a marked fall in the blood level (430 to 290 mg. per hundred cubic centimeters).

Massie and Miller[87] determined the size and shape of the heart by roentgenography in 16 patients who had had myocardial infarction. Films were taken at the bedside with patients in the sitting position on the third, fifth, twelfth and twenty-eighth days and during the third and sixth months. No consistent change in cardiac size was observed. In the two weeks following the infarction only 4 patients showed a demonstrable alteration in the size of the heart, which was increased in 2 and decreased in the other 2. Eight patients showed no change in the six month period. The alterations observed in the pulmonary fields were of interest in that 12 patients showed pulmonary congestion in the first one to two weeks, with the presence of basal rales by auscultation in only 7.

Many patients with angina pectoris complain of characteristic substernal oppression in the absence of the usual precipitating factors. In some a reflex mechanism initiated by disease in the gastrointestinal tract (cardiospasm, hiatus hernia, disease of the gallbladder, ulcer) can be demonstrated.

Harrison and Finks[88] present evidence to show that disturbed carbohydrate metabolism is another disorder which may precipitate various manifestations referable to the cardiovascular system. Characteristic features of such a mechanism are the appearance of symptoms two or more hours after meals, with relief following the injection of dextrose, and reproduction of symptoms following administration of insulin. The

83. White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of 500 Cases of the Former Condition, and of 200 Cases of the Latter, Am. Heart J. **7**:1, 1931.

84. English, J. P., and Willius, F. A.: Hemorrhagic Lesions of the Coronary Arteries, Arch. Int. Med. **71**:594 (May) 1943.

85. Steiner, A., and Domanski, R.: Serum Cholesterol Level in Coronary Arteriosclerosis, Arch. Int. Med. **71**: 397 (March) 1943.

86 Engelberg, H., and Newman, B. A.: Xanthomatosis: A Cause of Coronary Artery Disease in Young Adults, J. A. M. A. **122**:1167 (Aug. 21) 1943.

87. Massie, E., and Miller, W. C.: The Heart Size and Pulmonary Findings During Acute Coronary Thrombosis, Am. J. M. Sc. **206**:353, 1943.

88. Harrison, T. R., and Finks, R. M.: Glucose Deficiency as a Factor in the Production of Symptoms Referable to the Cardiovascular System, Am. Heart J. **26**:147, 1943.

authors refer to the state which produces these symptoms as "relative hypoglycemia," because the blood sugar values of the patients studied were usually within the limits of normal or only slightly abnormal. In many cases studied the subjective and objective reactions were similar to those commonly seen in cardiac neurosis. However, attacks of angina pectoris at rest were seen in those with typical effort angina.

Lesser [89] reports further observations on the action of testosterone propionate in the treatment of angina pectoris. Favorable results were obtained in every one of 22 patients with angina. A control series of patients who received sesame oil showed no improvement. After treatment was initiated, an average of twenty-eight days elapsed before improvement was noted, and a period of forty-three days elapsed before this became marked.

On the other hand, Levine and Likoff,[90] after a trial of the drug in 19 patients, were unable to conclude that it had any beneficial effect. Five of the 19 patients observed reported definite improvement, but the authors believed that this could be accounted for by the vagaries of the disease. Eleven patients reported no change whatever after four weeks of treatment with a dose of 25 mg. three times weekly.

CONGESTIVE HEART FAILURE

Although the clinical manifestations of congestive heart failure are well known, the exact mechanism of production is still a matter of controversy. Evidence is accumulating to discount as the only factor a simple mechanical basis for heart failure, in which peripheral venous congestion is said to indicate disproportionate failure of the right ventricle.

Starr, Jeffers and Meade [91] report results of acute and chronic experiments on the right side of the heart in dogs in which only slight changes of venous pressure followed extensive damage to the right side of the heart. In the acute experiments the right ventricle was damaged with a cautery, and in the chronic experiments vessels supplying the right side of the heart were ligated. They concluded that the mechanical factors directly connected with weakness of the right side of the heart are less important in the production of elevated venous pressure than tone of the blood vessels and other factors concerned with blood volume. It is hardly necessary to point out that the results of these experiments on animals are not wholly transferable to human patients.

Further observations on this problem carried out on human beings are reported by Warren and Stead,[92] in which peripheral accumulation of fluid in heart failure was observed before the venous pressure rose above normal levels. Both articles stress the fact that the knowledge of the dynamics of venous congestion in man is still far from complete.

Fahr and Buehler [93] attempted accurate quantitative definition of acute congestive heart muscle failure in physiologic terms. Their studies were carried out on heart-lung preparations. Their conclusions, in some contrast to those of Starr, Jeffers and Meade,[91] were

> The cardinal features of spontaneous heart failure or that produced by chloroform, chloral hydrate, alcohol and diphtheria toxin are (*a*) a decrease in mechanical efficiency of the heart, (*b*) dilatation of the ventricles, (*c*) a rise of the venous pressure in the right and left auricles, (*d*) a tendency toward decrease in the minute output of the ventricles.

All of the articles reviewed in this section contain a discussion of these controversial points and references for suggested reading.

LaDue and Fahr [94] investigated the effect of intravenous administration of lanatoside C on heart failure in the presence of normal sinus rhythm in human beings. Kymographic measurements of the size of the heart were made by the method of Keys and Friedell.[95] The limitations of this method are recognized, that is, the stroke volume of the left ventricle may not be numerically exact, but it is felt that reliable indexes of direction or magnitude of any change in the output of the heart can be obtained by

89. Lesser, M. A.: Treatment of Angina Pectoris with Testosterone Propionate, New England J. Med. **228**:185, 1943.

90. Levine, S. A., and Likoff, W. B.: The Therapeutic Value of Testosterone Propionate in Angina Pectoris, New England J. Med. **229**:770, 1943.

91. Starr, I.; Jeffers, W. A., and Meade, R. H.: The Absence of Conspicuous Increments of Venous Pressure After Severe Damage to the Right Ventricle of the Dog, with a Discussion of the Relation Between Clinical Congestive Failure and Heart Disease, Am. Heart J. **26**:291, 1943.

92. Warren, J. V., and Stead, E. A.: Fluid Dynamics in Chronic Congestive Heart Failure: An Interpretation of the Mechanisms Producing the Edema, Increased Plasma Volume, and Elevated Venous Pressure in Certain Patients with Prolonged Congestive Failure, Arch. Int. Med. **73**:138 (Feb.) 1944.

93. Fahr, G., and Buehler, M. S.: A Physiologic Definition of Acute Congestive Heart Muscle Failure, Am. Heart J. **25**:211, 1943.

94. LaDue, J. S., and Fahr, G.: The Effect of the Intravenous Administration of Lanatoside C upon the Output, Diastolic Volume, and Mechanical Efficiency of the Failing Human Heart, Am. Heart J. **25**:344, 1943.

95. Keys, A., and Friedell, H.: Measurement of the Stroke Volume of the Human Heart from Roentgenograms: Simultaneous Roentgenkymographic and Acetylene Rebreathing Experiments, Am. J. Physiol. **126**:741, 1939.

successful estimations of output from kymograms. The diastolic volume of normal and pathologic hearts can be ascertained accurately. The authors state:

The intravenous administration of lanatoside-C to patients with heart failure and normal sinus rhythm usually increases the pulse pressure and reduces circulation time and venous pressure within two hours. In ten such patients the diastolic heart volume was reduced in five and stroke volume was increased in eight. In the latter eight the product of the stroke output and the mean blood pressure was definitely increased, whereas the diastolic heart volume decreased or was unchanged. Since the latter is an index of oxygen consumption, these increases in work must have meant improvement in the mechanical efficiency of the hearts of eight out of the ten patients studied.

WAR MEDICINE

A large scale experiment has been carried out in the reexamination of 4,994 men rejected for military service because of the diagnosis of cardiovascular defects or neurocirculatory asthenia.[96] It is necessary to quote the conclusions almost in their entirety because of the complex nature of the study.

2. The chief reasons for the reexamination were to determine (*a*) the problems in cardiovascular diagnosis that particularly concern the range of the normal cardiovascular system with respect to service, (*b*) the possible salvage of men for the Army by reclassification as 1A, and (*c*) the comparison of opinions of cardiovascular experts with those of the examiners at local boards and induction stations to determine the desirability of such reexaminations in this or other special medical fields throughout the country.

3. Of the total number of 4,994 cardiovascular rejectees examined, there were 863 (17.3 per cent) resubmitted as 1A and 4,131 (82.7 per cent) whose rejection as 4F was confirmed.

4. The percentage of men resubmitted as 1A was quite similar in Boston (18.8 per cent),[97] New York (19.2 per cent), and Philadelphia (16.5 per cent). In San Francisco 28.6 per cent were resubmitted.[98] Chicago yielded the lowest salvage (3.88 per cent), apparently because of the fact that cardiovascular experts had already been freely used in the decision about doubtful cases, a procedure which might profitably be followed by other examining groups throughout the country.

5. The chief cause for rejection was rheumatic heart disease, found in 2,476 men, or 50 per cent of the total 4,994, and in 59.9 per cent of the final 4F group. Mitral valvular disease without aortic valvular disease was diagnosed in the majority of these rheumatic heart cases, 1,500, or 60.6 per cent (750 with obvious stenosis), aortic valvular disease without apparent mitral valve involvement in 280, or 11.3 per cent (72 aortic stenosis and 208 aortic regurgitation alone), and mitral and aortic valvular disease combined in the remaining 628, or 25.4 per cent. Auricular fibrillation complicating mitral stenosis was found in 24 of the cases. The incidence of rheumatic heart disease varied from 70.3 per cent of the rejectees in Chicago to 39.6 per cent in San Francisco.

6. The second most common cause for final rejection was hypertension, found in 1,059 cases (25.6 per cent of the 4F cases and 21 per cent of the total series). The majority showed elevation of both systolic and diastolic levels; a few had either systolic hypertension alone or diastolic hypertension alone. The incidence varied little from city to city but was relatively more common in the fourth than in the third decade.

7. Third in frequency as a cause of rejection was neurocirculatory asthenia with 204 cases (4.0 per cent of the total series, or 4.9 per cent of those finally labeled 4F). Negroes were rarely affected. The incidence varied from 78 (8 per cent) in Boston to 11 (1.1 per cent) in Chicago.

8. The fourth condition responsible for rejection of more than 100 men was sinus tachycardia; there were 189 cases, or 3.8 per cent of the entire group and 4.6 per cent of the final 4F cases. The numbers varied from 75 in Chicago to 8 in Philadelphia.

9. The fifth most common cause for rejection was congenital heart disease, found in 183 cases (4.4 per cent of the 4F cases). The abnormality most commonly diagnosed was ventricular septal defect (Roger's disease) in more than a third of all the cases, 73. Five other defects, in the order of their frequency, were patency of the ductus arteriosus (29 cases), pulmonary stenosis (13 cases and 2 more with the tetralogy of Fallot), coarctation of the aorta (14 cases), auricular septal defect (6 cases) and subaortic stenosis (5 cases). The city incidence varied from over 6 per cent (63 cases) in San Francisco to 1.8 per cent (18 cases) in Philadelphia.

10. Other causes for rejection include cardiac enlargement alone, determined by x-ray examination (76 cases), arrhythmia in 32, including 17 cases of paroxysmal tachycardia, 6 of uncomplicated auricular fibrillation, 2 of auricular flutter and 5 of auriculoventricular block; electrocardiographic abnormalities alone in another 32 cases including 10 with bundle branch block; cardiovascular syphilis in only 17 cases, thyrotoxicosis in 14, recent rheumatic fever in 13, cardiac strain from chest deformities in 10, coronary heart disease in only 6, pericarditis in 4, and peripheral vascular defects in 3. Unspecified heart disease was diagnosed in 113 cases.

11. A history of rheumatic fever was obtained in slightly over a fourth of all the cases of rheumatic heart disease (28.8 per cent in four of the cities) and in nearly half of those in Boston and New York. A history of chorea was rare (1.8 per cent of the rheumatic heart cases in these same four cities).

12. Although the great majority reexamined were white men there were a good many Negroes (something under 10 per cent, 386 out of 4,035 examined in four of the five cities) and a few Chinese and Filipinos. There was a high rejection rate for the Chinese and Filipinos (100 per cent) in the four cities in which racial data were available. Nine of the fifteen cases of

96. Levy, R. L.; Stroud, W. D., and White, P. D.: Report of Reexamination of 4,994 Men Disqualified for General Military Service Because of the Diagnosis of Cardiovascular Defects: A Combined Study Made by Special Medical Advisory Boards in Boston, Chicago, New York, Philadelphia and San Francisco, J. A. M. A. **123**:937 (Dec. 11); 1029 (Dec. 18) 1943.

97. "Another 11.4 per cent were considered 'borderline' in Boston but after special consideration were not resubmitted."

98. "The men resubmitted in San Francisco included a moderate number of 'borderline' cases, while in Chicago, New York and Philadelphia the majority of 'borderline' cases were rejected again."

aortic syphilis found in those cities were among Negroes, and hypertension was also more often found in the Negroes (38.5 per cent of the final 4F cases compared to 23.1 per cent for the white men). Rheumatic heart disease was evenly represented (63.8 per cent compared to 63.9 per cent), but neurocirculatory asthenia was very much less in the Negroes (0.9 per cent, compared to 5.5 per cent).

13. There were eight problems of particular interest which remain unsolved and should be the focus of follow-up study but concerning which tentative opinions were expressed: (*a*) the interpretation of apical systolic murmurs (may they, if very slight or even slight, in the absence of any other abnormal or doubtful finding, be considered inadequate reason for rejection?); (*b*) the upper limits of the normal blood pressure (may the systolic pressure in very nervous young men be set perhaps as high as 160 mm. of mercury or even a shade more, provided the diastolic pressure does not exceed 90 mm.?); (*c*) the limits of the normal pulse rate at rest (may there not be a wider range, say from 40 to 120 per minute, than that actually given in the current criteria?); (*d*) the heart size, which also varies widely, especially according to body build, and may perhaps in a few normal individuals exceed the standards set by Hodges and Eyster; (*e*) the electrocardiogram, of which the wide range of normal has not yet been explored adequately; (*f*) neurocirculatory asthenia, difficult to diagnose in mild degree, but probably rejectable even when slight, unless there is an obvious cause which can be corrected; (*g*) recent rheumatic fever, a hazard even when the heart seems perfectly normal, and (*h*) exercise tests, the usefulness of which, in cardiovascular examination for military service, is open to question.

14. A follow-up study of the men reclassified as 1A and especially of the doubtful "borderline" cases in the final 4F group should, in the years to come, aid in solving some of the various problems in cardiovascular diagnosis that still remain.

15. The wisdom of extending these reexaminations for the sake of the salvage alone is doubtful in view of the time required, the few expert examiners available, and the relatively small percentage of men reclassified as 1A; but the applications of the lessons learned in the course of this study should be helpful in future examinations.

Follow-up observations from New York, Boston and Chicago indicate that most of the men recommended as suitable for service with the armed forces have been inducted into service.

Several important papers relating to cardiovascular disease in wartime will appear during 1944.

MISCELLANEOUS

Gouley and Sickel [99] report a series of cases in which the pathologic observations point to a cause for aortic regurgitation which hitherto has not been stressed, although it has not escaped recognition. They comment on the occurrence of aortic regurgitation in patients in the older age groups, in whom syphilis, rheumatic heart disease, bacterial endocarditis or arteriosclerotic degeneration is not the etiologic factor. The 11 patients whose cases are reported showed the characteristic diastolic murmur of aortic regurgitation. Hypertension was present in most cases. The pathologic factors consisted of dilatation of the aortic ring with a characteristic valvular lesion consisting of sclerotic thickening of the midportion of the free margin of the leaflet without involvement of the commissures. The latter may be pulled apart, and the leaflets are frequently elongated. These changes are considered secondary to dilatation of the ring and are effected by the eroding action of flow leakage. Syphilis may coexist.

Weiss, Stead, Warren and Bailey [100] express the belief that scleroderma heart disease is a clinical and pathologic entity. Nine cases of generalized scleroderma were reported, with signs and symptoms of heart disease in each. Good evidence to show that none of the common etiologic factors contributed to the heart failure was presented. Autopsy observations (2 cases) were of special interest, in that scars of unusual type involving the myocardium primarily were found. These differed from ordinary vascular lesions in absence of significant abnormalities in the vessels, lack of hemosiderin deposits, inconstant relation to arteries and an unusual cellular character of the connective tissue itself. The frequent association of pulmonary lesions made the evaluation of cardiac symptoms difficult. All patients showed cardiac enlargement, dyspnea and edema. The electrocardiograms were abnormal in each case without consistent diagnostic patterns. It was concluded that in generalized scleroderma the heart, as well as the lungs and the gastrointestinal tract, may be involved.

Smith and Furth [101] report 5 cases of congestive failure of obscure origin in which the findings were similar to those in previously reported instances of Fiedler's myocarditis. Endocardial and myocardial fibrosis with cardiac hypertrophy and dilatation without change in the vessels or valves characterized the postmortem picture. In 3 cases mural thrombi were present, and in all cases widespread endocardial fibrosis in both ventricles was found. Because of a history of

99. Gouley, B. A., and Sickel, E. M.: Aortic Regurgitation Caused by Dilatation of the Aortic Orifice and Associated with a Characteristic Valvular Lesion, Am. Heart J. **26**:24, 194[illegible].

100. Weiss, S.; Stead, E. A., Jr.; Warren, J. V., and Bailey, O. T.: Scleroderma Heart Disease, Arch. Int. Med. **71**:749 (June) 1943.

101. Smith, J. J., and Furth, J.: Fibrosis of the Endocardium and the Myocardium with Mural Thrombosis, Arch. Int. Med. **71**:602 (May) 1943.

dietary deficiency in each instance the possibility of beriberi heart disease was considered, but no patient responded to thiamine chloride. Need for further definition of myocarditis of obscure origin is recognized.

Carter and Traut [102] investigated the incidence of angina pectoris in 300 patients with proved pernicious anemia. In only 3 could a definite diagnosis of angina be made. They were also interested in the incidence of symptoms and findings suggesting organic heart disease. Some manifestation was present in 257. Their conclusions were stated as follows:

> In the presence of severe anemia it is impossible to segregate dependably patients with primary cardiovascular involvement. All of the usual criteria of cardiovascular disease may occur solely as the result of anemia. These symptoms and findings are not restricted to any type of anemia or related to the severity of the anemia. Examination of the blood is essential for dependable differentiation. Cardiovascular manifestations often occur with hematologic decompensation and disappear after treatment or during a remission.

Paradoxic pulse, as measured by the sphygmomanometer, is seen in conditions other than constrictive pericarditis or pericardial tamponade. Osgood [103] observed that fluctuation as much as 30 mm. of mercury systolic may occur in paroxysms of bronchial asthma with decline of the level during inspiration and rise during expiration. In some patients this fluctuation varied directly with the intensity of the asthmatic paroxysm. This phenomenon was explained by following and amplifying the observations of Reid,[104] who stated that the lungs are more important than is generally realized in promoting the return of blood to the left side of the heart. In this conception the flow of blood in the pulmonary veins is considered an active propulsion, as in the squeezing of a sponge, rather than an aspiration. The propulsion takes place during expiration. During inspiration the blood is held in the lung. This mechanism is exaggerated in asthma by the greater negative intrathoracic pressure during inspiration, which may result in a more pronounced dilatation of veins. It it also considered that the expiratory "squeeze" is perhaps greater because of increased thoracic pressure at that time.

In several patients observed at the Massachusetts General Hospital after the Cocoanut Grove catastrophe asthma developed as a result of severe bronchiolitis, which in turn resulted from the irritant gases inhaled.[105] A definite pulsus paradoxicus was observed in 3 cases, although this does not appear in the report.

Osgood and Ehret [106] extended their observations on changes in blood pressure in asthma, with special reference to the effect of therapeutic drugs. After injection of epinephrine hydrochloride the respiratory fluctuation approached normal when relief from the asthmatic attack was obtained. After intravenous injection of theophylline ethylenediamine there was a decrease in fluctuation, but of lesser magnitude. This difference in result suggested a possible difference in action of the two drugs. The authors suggest that the bronchodilating effect of theophylline ethylenediamine may be of secondary importance. Its principal action is thought to be an increase of blood flow through the pulmonary circuit by vasodilation.

102. Carter, J. B., and Traut, E. F.: Cardiovascular Manifestations in Pernicious Anemia, Arch. Int. Med. **72**:757 (Dec.) 1943.

103. Osgood, H.: Blood Pressure Fluctuations in Bronchial Asthma, J. Lab. & Clin. Med. **28**:927, 1943.

104. Reid, W. D.: Respiration as a Factor in the Circulation of Blood, Ann. Int. Med. **17**:206, 1942.

105. Aub, J. C.; Pittman, H., and Brues, A. M.: Management of the Cocoanut Grove Burns at the Massachusetts General Hospital: The Pulmonary Complications; a Clinical Description, Ann. Surg. **117**:834, 1943.

106. Osgood, H., and Ehret, F. E.: Blood Pressure Fluctuations in Bronchial Asthma, J. Lab. & Clin. Med. **28**:1415, 1943.

INDEX TO VOLUME 73

Book Reviews are grouped together and are indexed under that heading in alphabetical order under the letter B.

Abnormalities and Deformities: See under names of organs and regions
Abscess: See under names of organs and regions, as Liver; etc.
Acid, Amino: See Amino Acids
  Ascorbic: See Ascorbic Acid
  Cevitamic: See Ascorbic Acid
  Cholic: See under Bile
  Nicotinic: See Nicotinic Acid
  Tannic: See Tannin
Acne, Halowax, 361
Adams, E.: Postoperative thrombocytosis, 329
Age, capillary fragility in relation to diabetes mellitus, hypertension and age, 18
Agglutinins and Agglutination: See also Blood, groups; Streptococci; etc.
  transfusion reactions caused by acquired intragroup incompatibilities, 199
Allergy: See Anaphylaxis and Allergy
Amebiasis, amebic hepatitis and hepatic abscess, 356
Amino Acids and diseases of digestive tract, 178
Analgesia: See Anesthesia; Pain
Anaphylaxis and Allergy: See also Asthma; Food, allergy; Hay Fever; etc.
  allergy in Army, 248
  allergy; review of literature of 1943, 248
  anaphylaxis, 259
  chemical effectors, 257
  gastrointestinal allergy, 180
  palindromic rheumatism; "new," oft recurring disease of joints (arthritis, periarthritis, paraarthritis) apparently producing no articular residues; report of 34 cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis, 293
Anemia, sickle cell, rate of sedimentation of erythrocytes in, 41
  stomach in, 98
Anesthesia, comparative study of analgesic effect of morphine sulfate and monoacetylmorphine, 322
Angina Pectoris, 493
Annegers, J. H.: Effect of cinchophen on secretion of cholic acid, 1
Antigens and Antibodies: See Agglutinins and Agglutination; Streptococci; etc.
Aorta, regurgitation, 497
Appendicitis, 158
Araya, E.: Influence of respiration on blood pressure in man with note on vasomotor waves, 29
Armed Forces Personnel: See Military Medicine; etc.
Armies: See Military Medicine
Arrhythmia, 478
  treatment of, 480
Arsenic and Arsenic Compounds: See Arsphenamines
Arsphenamines, effectiveness of various sulfonamide drugs and neoarsphenamine against pneumococci in bone marrow cultures; comparative study, 13
Arteries: See also Aorta; Arteriosclerosis; Blood pressure; Blood vessels; Embolism; Thrombosis; Vasomotor System; etc.
  coronary; coronary heart disease, 493
  Inflammation: See Endarteritis
Arteriosclerosis, oscillometric index; aid in evaluating arterial status of lower extremities, 241
Arthritis: See also Periarthritis; Rheumatism
  palindromic rheumatism; "new," oft recurring disease of joints (arthritis, periarthritis, paraarthritis) apparently producing no articular residues; report of 34 cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis, 293
Ascorbic Acid, vitamins A, B and C in diabetic children, 391
Asthenia in military medicine, 496
Asthma: See also Anaphylaxis and Allergy
  bronchial, spontaneous pneumothorax complicating; report of 2 cases and consideration of possible mechanisms involved in its production, 460
  bronchospasm associated with pulmonary embolism; respiratory failure, 403
  heart in, 252
  physiology and pathology, 251
  treatment of, 254
Atherosclerosis: See Arteriosclerosis
Atkinson, A. J.: Effect of cinchophen on secretion of cholic acid, 1
Auricular Fibrillation: See Arrhythmia
Ayer, G. D., Jr.: Transfusion reactions caused by acquired intragroup incompatibilities, 199

Bacilli: See Bacteria
Bacteria: See Streptococci; Viruses; etc.
  Cholerae Suis: See Salmonella
  Dysentery: See Dysentery
  Eberth's: See Typhoid
  Shigella: See Dysentery
  Streptococci: See Streptococci
Baer, S.: Studies in acute myocardial infarction; diagnosis and location of infarct by electrocardiogram, 286
Bagasse Disease: See Lungs, mycosis
Battro, A.: Influence of respiration on blood pressure in man with note on vasomotor waves, 29
Beams, A. J.: Experimental hypoproteinemia and edema; studies of intestinal absorption and intestinal roentgenologic characteristics, 397
Beaser, S. B.: Capillary fragility in relation to diabetes mellitus, hypertension and age, 18
  Vitamin therapy in increased capillary fragility of diabetes mellitus, 23
Bersack, S. R.: Hodgkin's disease; incidence and prognosis; statistical correlation with clinicopathologic picture, 232
Bile, effect of cinchophen on secretion of cholic acid, 1
Bile Ducts: See Biliary Tract; Gallbladder
Bilharziasis: See Schistosomiasis
Biliary Tract: See also Gallbladder; Liver
  diseases of liver and biliary tract; hepatic involvement in various diseases related to war, 349
Biopsy: See Liver
Bissell, G. W.: Thiamine metabolism with reference to role of liver and kidneys, 203
Bites: See Insects
Blood, Circulation: See also Arteries; Capillaries; Cardiovascular Diseases; Heart; Vasomotor System; etc.
  circulation, 477
  Diseases: See Anemia; etc.
  fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, 138
  Groups: See also Blood, transfusion
  groups; transfusion reactions caused by acquired intragroup incompatibilities, 199
  platelets; postoperative thrombocytosis, 329
  pressure, determination; oscillometric index; aid in evaluating arterial status of lower extremities, 241
  pressure, high; capillary fragility in relation to diabetes mellitus, hypertension and age, 18
  pressure, high; effects of unilateral nephrectomy in treatment of hypertension; evaluation, 123
  pressure, high; hypertension, 491
  pressure; influence of respiration on blood pressure in man with note on vasomotor waves, 29
  sedimentation rate of erythrocytes in sickle cell anemia, 41
  proteins; experimental hypoproteinemia and edema; studies of intestinal absorption and intestinal roentgenologic characteristics, 397

Blood—Continued
proteins; nutritional problems presented by patient with extensive jejunoileitis, 466
transfusion; new aid in control of hemorrhage in severe damage to liver; transfusions of blood fortified by administration of vitamin K to donors, 131
transfusion reactions caused by acquired intragroup incompatibilities, 199
Vessels: See also Arteries; Capillaries; Vasomotor System; etc.
vessels; palindromic rheumatism; "new," oft recurring disease of joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues; report of 34 cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis, 293
Bones: See also under names of bones
marrow; effectiveness of various sulfonamide drugs and neoarsphenamine against pneumococci in bone marrow cultures; comparative study, 13

Book Reviews:
Afecciones del endocardio: Contribucion al estudio anatomo clinico de las affecciones del endocardio; M. Perea Munoz, 198
Allergy in Practice; S. L. Feinberg, 364
Applied Dietetics; F. Stern, 269
Arthropathies; A. A. de Lorimier, 112
Blutersatzfrage im Felde; A. Fonio, 432
Borderline of Psychiatry; S. Cobb, 112
Clinical Lectures on Gallbladder and Bile Ducts; S. Weiss, 269
Clinical Significance of Blood in Tuberculosis; G. L. Muller, 431
Compleat Pediatrician; W. C. Davison, 269
Dysenteric Disorders; P. Manson-Bahr, 112
Elements of Medical Mycology; J. H. Swartz, 269
Elimination Diets and Patients' Allergies; A. H. Rowe, 432
Family Nutrition, 270
Frontiers in Cytochemistry: Physical and Chemical Organization of Cytoplasm; N. L. Hoerr, 198
Gastro-enterology; H. L. Bockus, 267, 364
Handbook of Nutrition: Symposium, prepared by Council on Foods and Nutrition of American Medical Association, 269
Hundred Years of Medicine; C. D. Haagensen and W. E. B. Lloyd, 111
Internal Medicine in General Practice; R. P. McCombs, 269
Laboratory Methods of United States Army; edited by J. S. Simmons and C. J. Gentzkow, 431
Manometric Methods as Applied to Measurement of Cell Respiration and Other Problems; M. Dixon, 112
Medical Physics; O. Glasser, 269
Miotonias; A. Lanari, 198
Modificacoes de forma do eletrocardiograma; D. Pazzanese, 268
Neurology; R. R. Grinker, 269
Office Treatment of Nose, Throat and Ear; A. R. Hollender, 268
Osler's Principles and Practice of Medicine; H. A. Christian, 364
Pain, 268
Pathology and Therapy of Rheumatic Fever; L. Lichtwitz, 267
Plants and Vitamins; W. H. Schopfer, 364
Primeras reuniones extraordinarias de la Asociacion de medicos del Hospital Durand; edited by J. A. Pique, 270
Publicaciones del Centro de Investigaciones Tisiologicas, 111
Role of Nutritional Deficiency in Nervous and Mental Disease, 267
Symposium on Chronic Diseases, in Medical Clinics of North America, 432
Synopsis of Clinical Syphilis; J. K. Howles, 112
Synopsis of Diseases of Heart and Arteries; G. R. Herrmann, 430
Synopsis of Neuropsychiatry; L. S. Selling, 431
Synopsis of Tropical Medicine; P. Manson-Bahr, 111
Terapeutica des los grandes sindromes digestivos; edited by C. B. Udaondo, 431

Book Reviews—Continued
Textbook of Medicine; edited by R. L. Cecil, 268
Tropical Nursing: Handbook for Nurses and Others Going Abroad; A. L. Gregg, 432
Vascular Responses in Extremities of Man in Health and Disease; D. I. Abramson, 432
Your Arthritis: What You Can Do About It; A. E. Phelps, 112

Bowels: See Intestines
Boyer, N. H.: Bronchospasm associated with pulmonary embolism; respiratory failure, 403
Brain, Diseases: See Encephalitis; Mental Diseases
late cerebral sequelae of rheumatic fever, 472
Morgagni-Stewart-Morel syndrome; report of case with pneumoencephalographic findings, 7
Bronchi, importance of bronchography in case of unresolved pneumonia, 444
Spasm: See Asthma
Bronchiectasis, importance of bronchography in cases of unresolved pneumonia, 444
Bronchography: See Bronchi
Browne, D. C.: Life expectancy after attack of myocardial infarction; report of case of survival for 19 years after coronary thrombosis, 290
Brownlee, I. E.: Effectiveness of various sulfonamide drugs and neoarsphenamine against pneumococci in bone marrow cultures; comparative study, 13
Bruetsch, W. L.: Late cerebral sequelae of rheumatic fever, 472
Bullowa, J. G. M.: Effectiveness of various sulfonamide drugs and neoarsphenamine against pneumococci in bone marrow cultures; comparative study, 13
Burch, G. E.: Rate of sedimentation of erythrocytes in sickle cell anemia, 41

Calculi: See Gallbladder, calculi
Cancer: See under names of organs and regions, as Intestines; Stomach; etc.
Capillaries: See also Blood vessels; Vasomotor System
fragility in relation to diabetes mellitus, hypertension and age, 18
vitamin therapy in increased capillary fragility of diabetes mellitus, 23
Cardiovascular Diseases: See also Blood vessels; Heart
in military medicine, 496
Cardiovascular System: See Arteries; Blood vessels; Heart; Vasomotor System; etc.
Chamberlain, F. L.: Electrocardiographic features associated with hyperthyroidism, 148
Chapman, W. P.: Comparative study of analgesic effect of morphine sulfate and monoacetylmorphine, 322
Chemotherapy: See also under names of diseases, as Meningitis; etc.
and specific infections, 184
Chest: See Thorax
Children, gastrointestinal disturbances in, 172
Chlorodiphenyl, Halowax acne, 361
Chloronaphthalene, Halowax acne, 361
Cholelithiasis: See Gallbladder, calculi
Cinchophen, effect on secretion of cholic acid, 1
Circulation: See Blood, circulation
Cirrhosis: See under Liver
Civin, H.: Oscillometric index; aid in evaluating arterial status of lower extremities, 241
Colitis, ulcerative, 169
Communicable Diseases: See Meningitis; etc.
Contratto, A. W.: Infectious mononucleosis; study of 196 cases, 449
Correction in transcript of article by Captain John E. Leach entitled "Effect of Roentgen Therapy on the Heart: A Clinical Study" (Arch. Int. Med. 72:715 [Dec.] 1943), 270
Cranium, Morgagni-Stewart-Morel syndrome; report of case with pneumoencephalographic findings, 7
Curry, J. J.: Bronchospasm associated with pulmonary embolism; respiratory failure, 403
Cysts: See under names of organs and regions

Dallis, N. P.: Electric shock therapy in general hospital, 336
Deficiency Diseases: See Diet and Dietetics; Nutrition; Vitamins; etc.

Dermatitis: See also Eczema
industrial, 259
Dermatomyositis, 271
Desautels, R.: Comparative study of analgesic effect of morphine sulfate and monoacetylmorphine, 322
Diabetes Mellitus, capillary fragility in relation to diabetes mellitus, hypertension and age, 18
vitamin therapy in increased capillary fragility of, 23
vitamins A, B and C in diabetic children, 391
Diaphragm, Hernia: See Hernia, diaphragmatic
Diarrhea: See Dysentery
Diet and Dietetics: See also Nutrition; Vitamins; etc.
nutritional problems presented by patient with extensive jejunoileitis, 466
use of synthetic diet for food allergy and typhoid, 341
Digestive System: See also Gastrointestinal Tract; Intestines; Stomach; etc.
diseases and amino acids, 178
gastroenterology; review of literature from July 1942 to July 1943, 53, 154
motor aspects, 53
thoracic pain and disturbances in upper part of digestive tract, 75
Diverticula: See Duodenum; Stomach
Dole, G.: Group A hemolytic streptococcus antibodies; study of simultaneous infection of large number of men by single type, 238
Donors: See Blood, transfusion
Drucker, W.: Comparative study of analgesic effect of morphine sulfate and monoacetylmorphine, 322
Drugs, generalized cutaneous reactions; drug allergy, 261
Duodenum, diverticulitis, 161
Ulcers: See Peptic Ulcer
unusual tumors of small bowel, 104
Dysentery, specific infections and chemotherapy, 184

Eczema, atopic, 263
Edema and experimental hypoproteinemia; studies of intestinal absorption and intestinal roentgenologic characteristics, 397
fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, 138
Electrocardiogram: See under Heart
Electrotherapy, electric shock therapy in general hospital, 336
Elîçabe, C. A.: Influence of respiration on blood pressure in man with note on vasomotor waves, 29
Embolism: See also Thrombosis
bronchospasm associated with pulmonary embolism; respiratory failure, 403
cerebral; late cerebral sequelae of rheumatic fever, 472
Encephalitis, late cerebral sequelae of rheumatic fever, 472
Endocarditis, bacterial, 489
subacute, associated with infection with spirillum; report of case, with repeated isolation of organism from blood, 415
Erythrocytes, Sedimentation: See Blood, sedimentation
Esophagus, atresia of, 77
tumors of, 77
Extremities, blood supply; oscillometric index; aid in evaluating arterial status of lower extremities, 241

Fever: See Malaria; Typhoid; etc.
Glandular: See Mononucleosis, Infectious
Rat Bite: See Rat Bite Fever
Fibrositis: See under Rheumatism
Finch, C. A.: Fatal spontaneous potassium intoxication in patients with uremia, 384
Fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, 138
Fogelson, S. J.: Treatment of gastroduodenal ulcerative disease with sodium alkyl sulfate; preliminary report, 212
Food: See also Diet and Dietetics; Nutrition; Vitamins; etc.
allergy; use of synthetic diet for food allergy and typhoid, 341
Frankel, H.: Studies in acute myocardial infarction; diagnosis and location of infarct by electrocardiogram, 286
Free, A. H.: Experimental hypoproteinemia and edema; studies of intestinal absorption and intestinal roentgenologic characteristics, 397
Frontal Bone, Morgagni-Stewart-Morel syndrome; report of case with pneumoencephalographic findings, 7

Gallbladder: See also Bile; Biliary Tract
calculi; intestinal obstruction from gallstones, 362
Gallstones: See Gallbladder, calculi
Gastric Ulcer: See Peptic Ulcer
Gastritis: See Stomach
Gastroenterology: See Gastrointestinal Tract
Gastrointestinal Tract: See also Digestive System; Intestines; Stomach; etc.
allergy, 180
and vitamins, 176
disturbances in children, 172
experimental hypoproteinemia and edema; studies of intestinal absorption and intestinal roentgenologic characteristics, 397
gastroenterology; review of literature from July 1942 to July 1943, 53, 154
miscellaneous conditions, 181
motor aspects, 53
physiologic aspects, 53
problems relating to war, 193
von Gierke's Disease: See under Glycogen
Gilbert, P. D.: Primary atypical pneumonia; report of 125 cases, with autopsy observations in 1 fatal case, 115
Glandular Fever: See Mononucleosis, Infectious
Glycogen, clinical significance of glycogen content of liver, 110
Glycosuria: See Diabetes Mellitus
Goldsmith, G. A.: Urinary excretion of nicotinic acid and its derivatives, 410
González Segura, R.: Influence of respiration on blood pressure in man with note on vasomotor waves, 29
Gordan, G.: Electrocardiographic features associated with hyperthyroidism, 148
Granuloma, Malignant: See Hodgkin's Disease
nutritional problems presented by patient with extensive jejunoileitis, 466
Greene, C. H.: Diseases of liver and biliary tract; hepatic involvement in various diseases related to war, 349
Grier, G. S., III: Importance of bronchography in cases of unresolved pneumonia, 444
Grill, J.: Clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, 433
Grossman, L. A.: Dermatomyositis, 271

Halowax: See Chlorodiphenyl; Chloronaphthalene
Hampton, S. F.: Use of synthetic diet for food allergy and typhoid, 341
Harford, C. G.: Use of synthetic diet for food allergy and typhoid, 341
Hay Fever, 248. See also Anaphylaxis and Allergy
Headache: See Migraine
Heart: See also Arrhythmia; Blood, circulation; etc.
abnormalities; congenital heart disease, 488
congestive heart failure, 495
coronary heart disease, 493
Diseases: See also Cardiovascular Diseases; Myocarditis; etc.
Diseases, Congenital: See Heart, abnormalities
diseases; review of significant contributions made during 1943, 477
electrocardiographic features associated with hyperthyroidism, 148
electrocardiography, 481
fatal spontaneous potassium intoxication in patients with uremia, 384

Heart—Continued
fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, 138
in asthma, 252
life expectancy after attack of myocardial infarction; report of case of survival for 19 years after coronary thrombosis, 290
roentgenology, 488
scleroderma heart disease, 497
studies in acute myocardial infarction; diagnosis and location of infarct by electrocardiogram, 286
Heldt, T. J.: Electric shock therapy in general hospital, 336
Hematology: See Blood
Hemorrhage, new aid in control in severe damage to liver; transfusions of blood fortified by administration of vitamin K to donors, 131
Hemostasis: See Blood, coagulation; Hemorrhage; etc.
Hench, P. S.: Palindromic rheumatism; "new," oft recurring disease of joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues; report of 34 cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis, 293
Hepatitis: See under Liver
Hernia, diaphragmatic, 78
Histamine, chemical effectors, 257
Hitzig, W. M.: Subacute endocarditis associated with infection with spirillum; report of case, with repeated isolation of organism from blood, 415
Hodgkin's Disease, incidence and prognosis; statistical correlation with clinicopathologic picture, 232
Hospitals, electric shock therapy in general hospital, 336
Hurst, D. D.: Electric shock therapy in general hospital, 336
Hydrocephalus, Morgagni-Stewart-Morel syndrome; report of case with pneumoencephalographic findings, 7
Hypertension: See Blood pressure, high
Hyperthyroidism: See Thyroid, hyperthyroidism
Hypertrophy: See under names of organs and regions

Icterus: See Jaundice
Heitis: See Intestines
Ileum: See under Intestines
Immunity: See Anaphylaxis and Allergy; etc.
Industry, bagasse disease of lungs, 365
Halowax acne, 361
industrial dermatitis, 259
industrial poisons and damage to liver, 360
Infarction: See under Heart
Infection: See under names of bacteria, as Streptococci; etc.
Ingelfinger, F. J.: Nutritional problems presented by patient with extensive jejunoileitis, 466
Insects, bites, 265
Insulin: See also Diabetes Mellitus
allergy, 265
Intestines: See also Duodenum; Gastrointestinal Tract
absorptive aspects, 72
cancer of large bowel, 163
Diseases: See also Dysentery
diseases; nutritional problems presented by patient with extensive jejunoileitis, 466
diseases; regional ileitis, 106
experimental hypoproteinemia and edema; studies of intestinal absorption and intestinal roentgenologic characteristics, 397
obstruction, 154
obstruction from gallstones, 362
other tumors of large intestine, 165
parasites, 166
unusual tumors of small bowel, 104
Ivy, A. C.: Effect of cinchophen on secretion of cholic acid, 1

Jager, B. V.: Dermatomyositis, 271
Jaundice, infectious, 549
Jejunum: See Intestines
Joints, palindromic rheumatism; "new," oft recurring disease of joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues; report of 34 cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis, 293
Jones, C. M.: Comparative study of analgesic effect of morphine sulfate and monoacetylmorphine, 322
Gastroenterology; review of literature from July 1942 to July 1943, 53, 154
Jorgenson, M.: Use of synthetic diet for food allergy and typhoid, 341

Kammer, W. F.: Transfusion reactions caused by acquired intragroup incompatibilities, 199
Kidneys, clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, 433
effect of unilateral nephrectomy in treatment of hypertension; evaluation, 123
fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, 138
thiamine metabolism with reference to role of liver and kidneys, 203
Killian, S. T.: Nutritional problems presented by patient with extensive jejunoileitis, 466
Kinsey, R. E.: New aid in control of hemorrhage in severe damage to liver; transfusions of blood fortified by administration of vitamin K to donors, 131
Kuzma, J. F.: Clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, 433

Leonards, J. R.: Experimental hypoproteinemia and edema; studies of intestinal absorption and intestinal roentgenologic characteristics, 397
Leptospirosis: See Spirochetosis
Leukocytes: See Mononucleosis, Infectious; etc.
Liebesman, A.: Subacute endocarditis associated with infection with spirillum; report of case, with repeated isolation of organism from blood, 415
Life expectancy after attack of myocardial infarction; report of case of survival for 19 years after coronary thrombosis, 290
Lithiasis: See Gallbladder, calculi
Liver: See also Biliary Tract
allergy to injectable liver extracts, 265
amebic hepatitis and hepatic abscess, 356
aspiration biopsy of, 352
cirrhosis in Manson's schistosomiasis, 354
damage and tetrachlorethane intoxication, 361
Diseases: See also Jaundice
diseases of liver and biliary tract; hepatic involvement in various diseases related to war, 349
effect of cinchophen on secretion of cholic acid, 1
function and malaria, 349
Glycogen: See under Glycogen
hepatic damage from tannic acid, 360
industrial poisons and damage to liver, 360
new aid in control of hemorrhage in severe damage to liver; transfusions of blood fortified by administration of vitamin K to donors, 131
thiamine metabolism with reference to role of liver and kidneys, 203
Loughlin, W. C.: Vitamins A, B and C in diabetic children, 391
Lungs: See also Bronchi; Respiration; Thorax; etc.
mycosis; bagasse disease of lungs, 365
Lymph Nodes: See Mononucleosis, Infectious; etc.
Lymphogranuloma, Hodgkin's: See Hodgkin's Disease

McHardy, G.: Life expectancy after attack of myocardial infarction; report of case of survival for 19 years after coronary thrombosis, 290
Malaria and liver function, 349
Malnutrition: See Nutrition
Marchand, J. F.: Fatal spontaneous potassium intoxication in patients with uremia, 384

Medicine, Military: See Military Medicine
Ménière's Disease: See Vertigo, aural
Meningitis, Salmonella cholerae suis meningitis; report of case and review of literature on Salmonella meningitis, 425
Meningococci: See under Meningitis
Mental Diseases, electric shock therapy in general hospital, 336
late cerebral sequelae of rheumatic fever, 472
Migraine and Ménière's disease, 264
Military Medicine: See also Recruits; etc.
allergy in Army, 248
cardiovascular diseases in, 496
diseases of liver and biliary tract; hepatic involvement in various diseases related to war, 349
gastrointestinal problems relating to war, 193
group A hemolytic streptococcus antibodies; study of simultaneous infection of large number of men by single type, 238
infectious jaundice, 349
liver function and malaria, 349
peptic ulcer in army, 194
primary atypical pneumonia; analysis of 738 cases occurring during 1942 at Scott Field, Ill., 217
transfusion reactions caused by acquired intragroup incompatibilities, 199
Mirsky, I. A.: Clinical significance of glycogen content of liver, 110
Monoacetylmorphine: See Anesthesia
Mononucleosis, Infectious; study of 196 cases, 449
Moore, M. T.: Morgagni-Stewart-Morel syndrome; report of case with pneumoencephalographic findings, 7
Morel-Morgagni-Stewart Syndrome: See Frontal Bone
Morgagni-Stewart-Morel Syndrome: See Frontal Bone
Morphea: See Scleroderma
Morphine Sulfate: See Anesthesia
Mosenthal, H. O.: Vitamins A, B and C in diabetic children, 391
Murphy, F. D.: Clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, 433
Mycosis: See under Lungs
Myocarditis, diffuse isolated, associated with dietary deficiency, 375
Myocardium: See Heart; Myocarditis

National Defense: See War
Needles, R. J.: Primary atypical pneumonia; report of 125 cases, with autopsy observations in 1 fatal case, 113
Neoarsphenamine: See Arsphenamines
Nephrectomy: See under Kidneys
Nephrosis: See Kidneys, diseases
Nervous System: See Brain; etc.
Neter, E. R.: Salmonella cholerae suis meningitis; report of case and review of literature on Salmonella meningitis, 425
Neuroses and Psychoneuroses: See Mental Diseases; etc.
Nicotinic Acid, urinary excretion of nicotinic acid and its derivatives, 410
Nitrogen, metabolism; nutritional problems presented by patient with extensive jejunoileitis, 466
Nitrotoluene, toxicity, 360
Nutrition: See also Diet and Dietetics; Food; Vitamins; etc.
diffuse isolated myocarditis associated with dietary deficiency, 375
nutritional problems presented by patient with extensive jejunoileitis, 466

Occupations: See Industry
Olmsted, W. H.: Use of synthetic diet for food allergy and typhoid, 341
Oscillometry: See Blood pressure, determination
Osgood, E. E.: Effectiveness of various sulfonamide drugs and neoarsphenamine against pneumococci in bone marrow cultures: comparative study, 13
Owen, C. A.: Primary atypical pneumonia; analysis of 738 cases occurring during 1942 at Scott Field, Ill., 217
Oxygen: See Respiration

Pain, comparative study of analgesic effect of morphine sulfate and monoacetylmorphine, 322
Parasites: See under Intestines
Patch Tests: See Anaphylaxis and Allergy
Peptic Ulcer, clinical ulcer, 86
experimental, 83
in army, 194
treatment of gastroduodenal ulcerative disease with sodium alkyl sulfate; preliminary report, 212
Periarthritis, palindromic rheumatism; "new," oft recurring disease of joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues; report of 34 cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis, 293
Peters, J. B.: Thiamine metabolism with reference to role of liver and kidneys, 203
Plotz, Ella Sachs Plotz Foundation for Advancement of Scientific Investigation, 109
Pneumococci: See Pneumonia
effectiveness of various sulfonamide drugs and neoarsphenamine against pneumococci in bone marrow cultures; comparative study, 13
Pneumonia, importance of bronchography in cases of unresolved pneumonia, 444
primary atypical; analysis of 738 cases occurring during 1942 at Scott Field, Ill., 217
primary atypical; report of 125 cases, with autopsy observations in 1 fatal case, 113
Pneumothorax, spontaneous, complicating bronchial asthma; report of 2 cases and consideration of possible mechanisms involved in its production, 460
Poisons and Poisoning: See under names of substances
Pollen: See Hay Fever
Polley, T. Z.: Clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, 433
Potassium, fatal spontaneous potassium intoxication in patients with uremia, 384
Proteins in Blood: See Blood, proteins
Pullen, R. L.: Bagasse disease of lungs, 365
Pulse: See Arrhythmia; Blood pressure; Heart

Rackemann, F. M.: Allergy; review of literature of 1943, 248
Rantz, L. A.: Group A hemolytic streptococcus antibodies; study of simultaneous infection of large number of men by single type, 238
Rat Bite Fever, subacute endocarditis associated with infection with spirillum; report of case, with repeated isolation of organism from blood, 415
Recruits: See also Military Medicine
allergy in Army, 248
cardiovascular diseases of, 496
Respiration, bronchospasm associated with pulmonary embolism; respiratory failure, 403
influence on blood pressure in man with note on vasomotor waves, 29
Rheumatic Fever: See also Rheumatism
late cerebral sequelae of, 472
rheumatic heart disease, 490
Rheumatism: See also Arthritis; Rheumatic Fever
palindromic; "new," oft recurring disease of joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues; report of 34 cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis, 293
Rinzler, S. H.: Oscillometric index; aid in evaluating arterial status of lower extremities, 241
Rosenberg, E. F.: Palindromic rheumatism; "new," oft recurring disease of joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues; report of 34 cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis, 293
Roth, B.: Comparative study of analgesic effect of morphine sulfate and monoacetylmorphine, 322
Royer, C.: Comparative study of analgesic effect of morphine sulfate and monoacetylmorphine, 322
Royer, M.: Value of determination of urobilin, 110

Rudy, A.: Capillary fragility in relation to diabetes mellitus, hypertension and age, 18
Vitamin therapy in increased capillary fragility of diabetes mellitus, 23

Salmonella cholerae suis meningitis; report of case and review of literature on Salmonella meningitis, 425
Schistosomiasis, Manson's, hepatic cirrhosis in, 354
Scleroderma heart disease, 497
Sclerosis: See Arteriosclerosis
Seligman, A. M.: Capillary fragility in relation to diabetes mellitus, hypertension and age, 18
Vitamin therapy in increased capillary fragility of diabetes mellitus, 23
Sensenbach, W.: Effects of unilateral nephrectomy in treatment of hypertension; evaluation, 123
Sensitization: See Anaphylaxis and Allergy
Serum: See Blood
Shigella Dysenteriae: for Dysentery
Shoch, D. E.: Treatment of gastroduodenal ulcerative disease with sodium alkyl sulfate; preliminary report, 212
Skin, Diseases: See Dermatitis
Snapp, F. E.: Effect of cinchophen on secretion of cholic acid, 1
Societies, Mississippi Valley Medical Society, 109
Sodeman, W. A.: Bagasse disease of lungs, 365
Sodium Alkyl Sulfate: See Peptic Ulcer
Soley, M. H.: Electrocardiographic features associated with hyperthyroidism, 148
Spirillum: See Spirochaeta
Spirochaeta, subacute endocarditis associated with infection with spirillum; report of case, with repeated isolation of organism from blood, 415
Spirochetosis, icterohemorrhagic; leptospiral jaundice (Weil's disease), 353
Splenectomy; postoperative thrombocytosis, 329
Stead, E. A., Jr.: Fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, 138
Sternum, Puncture: See Bones, marrow
Stewart-Morgagni-Morel Syndrome: See Frontal Bone
Stomach: See also Gastrointestinal Tract
cancer, 99
diverticula, 97
gastritis, 79
in anemia, 98
motility of, 53
noncancerous tumors of, 103
physiology, 53
secretory aspects, 64
syphilis, 98
thoracic pain and disturbances in upper part of digestive tract, 75
tuberculosis, 98
Ulcers: See Peptic Ulcer
Streptococci, group A hemolytic streptococcus antibodies; study of simultaneous infection of large number of men by single type, 238
Sulfonamides, clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, 433
effectiveness of various sulfonamide drugs and neoarsphenamine against pneumococci in bone marrow cultures; comparative study, 13
reaction to, 262
Surgery, postoperative thrombocytosis, 329
Syphilis: See under names of organs and regions, as Stomach; etc.

Tannin, hepatic damage from tannic acid, 360
Tetrachlorethane, toxicity, 361
Thiamine, diffuse isolated myocarditis associated with dietary deficiency, 375
metabolism with reference to role of liver and kidneys, 203
vitamins A, B and C in diabetic children, 391
Thorax: See also Heart; Lungs; etc.
thoracic pain and disturbances in upper part of digestive tract, 75
Throat, infections; group A hemolytic streptococcus antibodies; study of simultaneous infection of large number of men by single type, 238
Thrombocytosis: See Blood, platelets
Thrombosis: See also Embolism
coronary heart disease, 493
life expectancy after attack of myocardial infarction; report of case of survival for 19 years after coronary thrombosis, 290
Thyroid, hyperthyroidism, electrocardiographic features associated with, 148
Toreson, W. E.: Diffuse isolated myocarditis associated with dietary deficiency, 375
Travell, J.: Oscillometric index; aid in evaluating arterial status of lower extremities, 241
Trinitrotoluene: See Nitrotoluene
Trowbridge, M., Jr.: Spontaneous pneumothorax complicating bronchial asthma; report of 2 cases and consideration of possible mechanisms involved in its production, 460
Tuberculosis: See under names of organs and regions, as Stomach; etc.
Tumors: See under names of organs and regions, as Duodenum; Esophagus; Intestines; Stomach; etc.
Typhoid, use of synthetic diet for food allergy and typhoid, 341

Ulcers, Peptic: See Peptic Ulcers
Uremia, fatal spontaneous potassium intoxication in patients with uremia, 384
Urine, urinary excretion of nicotinic acid and its derivatives, 410
Urobilin, value of determination of, 110

Vasomotor System: See also Arteries; Blood vessels; Capillaries; etc.
influence of respiration on blood pressure in man with note on vasomotor waves, 29
Veins: See Blood vessels; Extremities, blood supply; Thrombosis; Vasomotor System; etc.
Venous Pressure: See Blood pressure
Vertigo, aural; Ménière's disease and migraine, 264
Viruses, primary atypical pneumonia; report of 125 cases, with autopsy observations in 1 fatal case, 113
Vitamins: See also Ascorbic Acid; Nicotinic Acid; Thiamine
A, B and C in diabetic children, 391
and gastrointestinal tract, 176
B_1: See Thiamine
C: See Ascorbic Acid
K; new aid in control of hemorrhage in severe damage to liver; transfusions of blood fortified by administration of vitamin K to donors, 131
therapy in increased capillary fragility of diabetes mellitus, 23

War: See also Military Medicine; etc.
diseases of liver and biliary tract; hepatic involvement in various diseases related to war, 349
gastrointestinal problems relating to, 193
Warren, J. V.: Fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure, 138
Weil's Disease: See Spirochetosis, icterohemorrhagic
White, P. D.: Diseases of heart; review of significant contributions made during 1943, 477
Williams, C.: Diseases of heart; review of significant contributions made during 1943, 477
Williams, R. H.: Thiamine metabolism with reference to role of liver and kidneys, 203
Winsor, T.: Rate of sedimentation of erythrocytes in sickle cell anemia, 41